In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: January 11, 2023

CHRISTINA MITCHELL,	*	PUBLISHED
Petitioner,	*	No. 19-1534V
v.	*	Special Master Nora Beth Dorsey
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Ruling on Entitlement; Influenza ("Flu") Vaccine; Immune Thrombocytopenia Purpura ("ITP").
Respondent.	*	

David John Carney, Green & Schafle LLC, Philadelphia, PA, for Petitioner.
Andrew Henning, U.S. Department of Justice, Washington, DC, for Respondent.

RULING ON ENTITLEMENT[1]

I. INTRODUCTION

On October 2, 2019, Christina Mitchell ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"), 42 U.S.C. § 300aa-10 et seq. (2012).[2] Petitioner alleges that she suffered chronic immune thrombocytopenia purpura ("ITP") as the result of an influenza ("flu") vaccination administered on October 9, 2016. Petition at Preamble (ECF No. 1). Respondent argued against

[1] Because this Ruling contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the Ruling will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2012). All citations in this Ruling to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

compensation, stating that "an award of compensation under the [Vaccine] Act is not appropriate." Respondent's Report ("Resp. Rept.") at 1 (ECF No. 25).

After carefully analyzing and weighing the evidence presented in this case in accordance with the applicable legal standards, the undersigned finds that Petitioner has provided preponderant evidence that her flu vaccine caused her ITP, satisfying Petitioner's burden of proof under Althen v. Secretary of Health & Human Services, 418 F.3d 1274, 1280 (Fed. Cir. 2005). Accordingly, Petitioner is entitled to compensation.

II. ISSUES TO BE DECIDED

Diagnosis is not at issue. The parties' experts agree that the proper diagnosis is ITP. Joint Pre-Hearing Submission ("Joint Submission"), filed May 6, 2022, at 1 (ECF No. 68). More specifically, the parties agree Petitioner has been diagnosed with chronic ITP. Id. The parties do not dispute that Petitioner received a flu vaccine on October 9, 2016. Id. However, the parties dispute the onset of Petitioner's ITP. Id.

Petitioner does not allege a Table injury, and thus, Petitioner must prove causation-in-fact in accordance with Althen by preponderant evidence. Petitioner submitted two expert reports and supporting medical literature as evidence that molecular mimicry is the mechanism by which the flu vaccine can cause ITP. Petitioner's Motion for Ruling on the Record ("Pet. Mot."), filed May 6, 2022, at 27-40 (ECF No. 71). Petitioner's expert, Dr. Marc Serota, opines that the flu vaccine Petitioner received on October 9, 2016 caused her ITP. Id. at 43. Petitioner argues that because "there were no other causal agents that preceded the onset of ITP except for the [flu] vaccination, there exists a logical sequence of cause and effect that is supported by expert opinion." Id. Lastly, Petitioner alleges she developed ITP within 35 days of receiving her flu vaccination. Id. at 41-42. "Based on the evidence that exists in this case and the medical literature that currently exists, Petitioner has more than carried her burden of proof and should be entitled to compensation under the Vaccine Act." Id. at 48.

Respondent disagrees with Petitioner and argues Petitioner has not proven the Althen prongs by preponderant evidence. Resp. Response to Pet. Mot. ("Resp. Response"), filed June 24, 2022, at 10-20 (ECF No. 76). Respondent argues that Petitioner (1) "has [] not established a persuasive medical theory causally connecting the flu vaccine to ITP," (2) "has not established a logical sequence of cause and effect showing that the flu vaccine was the reason for her ITP," and (3) "has not demonstrated a proximate temporal relationship between the flu vaccine and her alleged injury." Id.

III. BACKGROUND

A. Medical Terminology

Immune thrombocytopenia,[3] also referred to as immune thrombocytopenia purpura or idiopathic thrombocytopenia purpura,[4] "is an acquired thrombocytopenia caused by autoantibodies against platelet antigens." Pet. Exhibit ("Ex.") 20(aa) at 1.[5]

"Adult chronic [ITP] is an autoimmune disorder manifested by immune-mediated thrombocytopenia. It manifests clinically by varying degrees of purpura[6] and mucosal bleeding depending in large part on the severity of the thrombocytopenia." Pet. Ex. 17(a) at 1.[7] Additional manifestations include petechiae,[8] epistaxis,[9] and severe hemorrhage. Pet. Ex. 20(aa)

[3] Thrombocytopenia is a "decrease in the number of platelets." Thrombocytopenia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=49875 (last visited Dec. 27, 2022).

[4] To avoid confusion, the undersigned will refer to immune thrombocytopenia, idiopathic thrombocytopenia purpura, and immune thrombocytopenia purpura as ITP throughout this Ruling.

[5] Donald M. Arnold & Adam Cuker, Immune Thrombocytopenia (ITP) in Adults: Clinical Manifestations and Diagnosis, UpToDate, https://www.uptodate.com/contents/immune-thrombocytopenia-itp-in-adults-clinical-manifestations-and-diagnosis (last updated July 2, 2020).

[6] Purpura is "any of a group of conditions characterized by ecchymoses or other small hemorrhages in the skin, mucous membranes, or serosal surfaces," or "any of several conditions similar to the traditional purpura group, which may be caused by decreased platelet counts[] [or] platelet abnormalities." Purpura, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=42170 (last visited Dec. 27, 2022).

[7] Robert McMillan et al., Self-Reported Health-Related Quality of Life in Adults with Chronic Immune Thrombocytopenic Purpura, 83 Am. J. Hematology 150 (2008).

[8] Petechia is "a pinpoint, nonraised, perfectly round, purplish red spot caused by intradermal or submucous hemorrhage." Petechia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=38200 (last visited Dec. 27, 2022).

[9] Epistaxis is a nosebleed or "hemorrhage from the nose." Epistaxis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=16952 (last visited Dec. 27, 2022).

at 7-9. "The clinical presentation of ITP is defined [as] less than 100,000 platelets per µl . . . ." Pet. Ex. 17(d) at 1;[10] see also Resp. Ex. H at 2.[11]

ITP can be classified as either primary or secondary. Resp. Ex. H at 2. Primary ITP is defined as "an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count < 100 $\times 10^9$/L) in the absence of other causes or disorders that may be associated with thrombocytopenia." Id. Secondary ITP is all other forms of immune-mediated thrombocytopenia that are due to underlying diseases such as systemic lupus erythematosus. Id.; Pet. Ex. 20(aa) at 2.

"[A]n ITP diagnosis . . . should be regarded as persistent if it lasts between three and 12 months, including patients without a spontaneous recovery or those lacking a complete response to treatment." Pet. Ex. 17(d) at 2; see also Resp. Ex. H at 3. After 12 months from the diagnosis, ITP is considered chronic. Pet. Ex. 17(d) at 2. ITP is considered "severe" if "bleeding occurs at the onset or later, requiring treatment adjustment and additional medical care." Id.

Both infections and vaccinations have been associated with the development of ITP. See, e.g., Pet. Ex. 17(d) at 3-9; Pet. Ex. 17(e) at 4-7;[12] Pet. Ex. 33 at 6;[13] Resp. Ex. K at 3;[14] Resp. Ex. Q at 3-4.[15] Associated infections include *Helicobacter pylori* ("*H. pylori*"), hepatitis C virus, human immunodeficiency virus ("HIV"), Epstein-Barr virus ("EBV"), cytomegalovirus, upper respiratory infections, sinusitis, tonsillitis, and chickenpox. Pet. Ex. 17(d) at 3-9; Pet. Ex. 33 at 6; Resp. Ex. K at 3; Resp. Ex. Q at 3. There is also an increased risk of ITP following the

[10] M. Rinaldi et al., Immune Thrombocytopaenic Purpura: An Autoimmune Cross-Link Between Infections and Vaccines, 23 Lupus 554 (2014).

[11] Francesco Rodeghiero et al., Standardization of Terminology, Definitions and Outcome Criteria in Immune Thrombocytopenic Purpura of Adults and Children: Report from an International Working Group, 113 Blood 2386 (2009).

[12] Carlo Perricone et al., Immune Thrombocytopenic Purpura (ITP) Associated with Vaccinations: A Review of Reported Cases, 60 Immunologic Rsch. 226 (2014).

[13] Nichola Cooper & James Bussel, The Pathogenesis of Immune Thrombocytopaenic Purpura, 133 Brit. J. Haematology 364 (2006).

[14] Maurice Swinkels et al., Emerging Concepts in Immune Thrombocytopenia, 9 Frontiers Immunology 1 (2018).

[15] Bernward Zeller et al., Childhood Idiopathic Thrombocytopenic Purpura in the Nordic Countries: Epidemiology and Predictors of Chronic Disease, 94 Acta Paediatrica 178 (2005).

measles-mumps-rubella ("MMR") vaccination.[16] Pet. Ex. 17(c) at 1;[17] Pet. Ex. 17(d) at 2; Pet. Ex. 17(q) at 1.[18] ITP has also been reported following vaccination for hepatitis A and B, diphtheria-tetanus-acellular pertussis ("DTaP"), varicella, and flu. Pet. Ex. 17(d) at 2; Pet. Ex. 17(e) at 4.

B. Procedural History

Petitioner filed her petition on October 2, 2019, followed by medical records on October 14, 2019. Petition; Pet. Exs. 1-8. This case was reassigned to the undersigned on October 23, 2019. Notice of Reassignment dated Oct. 23, 2019 (ECF No. 9). Petitioner filed additional medical records from February 2020 to June 2020. Pet. Exs. 9-14. On June 25, 2020, Respondent filed his Rule 4(c) Report, in which he recommended against compensation. Resp. Rept. at 1.

Petitioner filed expert reports from Dr. Abhimanyu Ghose and Dr. Serota along with supporting medical literature on December 24, 2020. Pet. Exs. 15-20. On April 27, 2021, Respondent filed expert reports and medical literature from Dr. Lisa Baumann Kreuziger and Dr. Neil Romberg. Resp. Exs. A-BB. Thereafter, the undersigned held a Rule 5 conference on August 12, 2021. Order dated Aug. 12, 2021 (ECF No. 48). The undersigned preliminarily found Petitioner's onset to be 35 days following her vaccination and that Petitioner would be able to satisfy all three Althen prongs. Id. at 2.

Petitioner filed additional medical records on October 12, 2021. Pet. Ex. 21. After the parties were unable to resolve this case informally, a status conference was held on January 11, 2022, and Petitioner was directed to file additional records. Order dated Jan. 11, 2022 (ECF No. 58). In January and March 2022, Petitioner filed additional medical records and an affidavit. Pet. Exs. 22-32. In May 2022, Petitioner filed additional medical literature. Pet. Exs. 33-35.

On March 12, 2022, Petitioner filed a joint status report, indicating both Petitioner and Respondent would like to resolve entitlement through a ruling on the record, and a briefing schedule was set. Joint Status Rept., filed Mar. 12, 2022, at 1 (ECF No. 65); Ruling on the Record Order dated Mar. 14, 2022 (ECF No. 66). On May 6, 2022, Petitioner filed a motion for a ruling on the record and Respondent filed the parties' joint submission. Pet. Mot.; Joint Submission. Respondent filed his response to Petitioner's motion on June 24, 2022, and Petitioner filed a reply on July 8, 2022. Resp. Response; Pet. Reply Brief in Support of Pet. Mot. ("Pet. Reply"), filed July 8, 2022 (ECF No. 77).

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[16] A presumption of causation is afforded under the Vaccine Injury Table for cases of ITP following MMR if onset is between 7 and 30 days. 42 C.F.R. § 100.3(a)(V)(A).

[17] E. Miller et al., Idiopathic Thrombocytopenic Purpura and MMR Vaccine, 84 Archives Diseases Childhood 227 (2001).

[18] Corri Black et al., MMR Vaccine and Idiopathic Thrombocytopaenic Purpura, 55 Brit. J. Clinical Pharmacology 107 (2003). This article was also cited by both of Petitioner's experts. See also Pet. Ex. 20(q).

This matter is now ripe for adjudication.

C. Factual History

1. Medical History

Prior to the vaccination at issue, Petitioner had a medical history that included annual examinations, acute pharyngitis, acute bronchitis, strep throat, and upper respiratory infections. Pet. Ex. 8 at 2-13; Pet. Ex. 9 at 1-7. On September 12, 2013, Petitioner went in for an annual appointment with her OB/GYN. Pet. Ex. 12 at 6. At this appointment, her platelet count was below normal at 137,000 (range 155,000-379,000). Id. at 7.

On October 9, 2016, Petitioner received the flu vaccination at issue; the Fluarix vaccine, a trivalent flu vaccine. Pet. Ex. 1 at 3. On October 21, 2016, Petitioner saw her OB/GYN for her annual visit. Pet. Ex. 3 at 11-12. Petitioner reported she felt dizzy during her menstrual period and headaches the week prior. Id. She reported no other abnormalities during this appointment. Id.

Petitioner had an appointment on December 7, 2016 with her OB/GYN due to a prolonged, heavy period. Pet. Ex. 3 at 8. She reported heavy bleeding for eight days, passing clots, and feeling dizzy. Id. Nurse practitioner, Elizabeth Newsome, performed a general examination and noted no abnormalities. Id. She sent Petitioner for blood work including a complete blood count ("CBC") to confirm anemia. Id. She advised Petitioner to take an over-the-counter iron supplement. Id. During this visit, Petitioner also reported cold-like symptoms and was prescribed a Z-Pak[19] to treat sinusitis. Id. The following day, on December 8, 2016, Petitioner's lab results came back showing a platelet count of 12,000 (range 150,000-400,000). Id. at 13-14. Petitioner was advised her platelet count was critically low and she needed to see a hematologist immediately. Id. at 13.

Dr. Gautam Kishore Kale, a hematologist-oncologist, evaluated Petitioner on December 12, 2016. Pet. Ex. 4 at 5. Dr. Kale noted Petitioner's recent sinus infection and diagnosed Petitioner with "[s]evere thrombocytopenia likely immune thrombocytopenia versus thrombocytopenia due to recent upper respiratory tract infection." Id. at 12. He noted that her ITP "[c]ould be from an acute viral upper respiratory infection which hopefully will improve over time and not cause chronic ITP." Id. During this appointment, Petitioner also complained of increased clumsiness and cognitive slowing. Id. Dr. Kale sent Petitioner for a computerized tomography ("CT") that showed no evidence of bleeding, however there was a 12 mm area of

[19] Z-pak, or Zithromax or azithromycin, is "an azalide antibiotic . . . used in the treatment of mild to moderate infections caused by susceptible organisms." Azithromycin, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=5244 (last visited Dec. 27, 2022); see also Zithromax, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=54062 (last visited Dec. 27, 2022).

high density that Dr. Kale postulated was calcium or a meningioma.[20] Id. at 12, 24. He did not find it to be of concern and determined her symptoms could be from her upper respiratory infection. Id. An ultrasound of her abdomen showed increased spleen size. Id. at 12. Petitioner was prescribed prednisone[21] to increase her platelet count. Id.

On December 19, 2016, Petitioner was seen for a follow up appointment. Pet. Ex. 4 at 18. Her platelet count had increased to 126,000. Id. at 24. Dr. Kale's assessment was again "severe thrombocytopenia likely immune thrombocytopenia versus thrombocytopenia due to recent viral upper respiratory tract infection." Id. He decided to taper her prednisone and monitor her platelet count weekly with the hope that her ITP was not chronic and would improve over time. Id. at 25.

After beginning the taper, Petitioner was seen for a follow up visit on December 27, 2016. Pet. Ex. 4 at 27, 30. Her platelet count had dropped to 32,000. Id. at 30, 33. Dr. Kale increased her prednisone to 40 mg per day. Id. at 34.

On January 3, 2017, Petitioner was seen for another follow up appointment. Pet. Ex. 4 at 35. Her platelet count was stable at 42,000 on 40 mg of prednisone. Id. at 38, 42. Based on this, Dr. Kale opined that Petitioner's thrombocytopenia appeared to be steroid dependent. Id. at 42. Dr. Kale and Petitioner discussed other treatment options including high dose dexamethasone[22] and a slow prednisone taper, Rituxan,[23] or a splenectomy.[24] Id. Petitioner wanted to stop taking steroids because they made her feel "a little edgy" and gain weight. Id. Petitioner decided to consider these options and continue taking prednisone. Id. On January 10, 2017, Petitioner was seen for another follow up appointment. Id. at 45. Petitioner had decided to start Rituxan and continue taking prednisone until Rituxan became effective. Id. at 51.

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[20] Meningioma is "a benign, slow-growing tumor of the meninges." Meningioma, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=30336 (last visited Dec. 27, 2022).

[21] Prednisone is "a synthetic glucocorticoid derived from cortisone, administered orally as an anti-inflammatory and immunosuppressant in a wide variety of disorders." Prednisone, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=40742 (last visited Dec. 27, 2022).

[22] Dexamethasone is administered as "an antiinflammatory and immunosuppressant in a wide variety of disorders." Dexamethasone, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=13599 (last visited Dec. 27, 2022).

[23] Rituxan is used "in the treatment of CD20-positive, B-cell noon-Hodgkin lymphoma; administered intravenously." Rituximab, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=43977 (last visited Dec. 27, 2022).

[24] Splenectomy is the "excision . . . of the spleen." Splenectomy, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=46675 (last visited on Dec. 27, 2022).

Petitioner was seen again on February 6, 2017. Pet. Ex. 4 at 53. Her diagnosis was "isolated thrombocytopenia likely ITP." Id. at 56. Petitioner was tapering off prednisone and was taking 30 mg and reducing by five mg every five to seven days. Id. She had received three of her four doses of Rituxan and was receiving her final dose that day. Id. Her platelet count had dropped to 11,000 the previous week. Id. at 57. She had then received high dose dexamethasone and her platelet count had increased to 183,000. Id. She had another follow up appointment on February 13, 2017. Id. at 62. After tapering her prednisone to 20 mg per day, Petitioner's platelet count dropped to 9,000 and she experienced epistaxis (nosebleed). Id. at 68. Her prednisone was increased to 60 mg per day. Id. at 69. She agreed to be admitted to the hospital for intravenous immune globulin ("IVIG")[25] and to start Nplate.[26] Id.

The next follow up appointment was March 1, 2017. Pet. Ex. 4 at 71. Petitioner had responded well to IVIG and Nplate. Id. at 77. Her platelet count was up to 191,000. Id. Dr. Kale explained to Petitioner that IVIG may remain effective for two-to-four weeks and since she was two weeks post-treatment, he would continue to monitor her platelets closely. Id. at 77-78. Dr. Kale tapered Petitioner's prednisone to 15 mg a day and then recommended continuing the taper with 10 mg per day for one week before stopping completely. Id. at 78. Dr. Kale's assessment at that visit was "severe labile immune thrombocytopenia (ITP)."[27] Id. at 77. At this visit, Dr. Kale did not reference a viral infection as the cause of Petitioner's ITP.

Petitioner was seen for another follow up on March 15, 2017. Pet. Ex. 4 at 79. Petitioner was down to 10 mg of prednisone and received Nplate 2 mcg/kg. Id. at 85. By her appointment on March 30, 2017, Petitioner was off prednisone and her platelet count was at 101,000. Id. at 95. Petitioner continued to receive weekly Nplate treatments. Id. Again, Dr. Kale's diagnosis was "severe labile immune thrombocytopenia (ITP)." Id.

From April 2017 to July 2017, Petitioner's platelet counts remained stable. Pet. Ex. 4 at 97-130. In August, her platelet count decreased to 50,000 "in the setting of an [upper respiratory tract infection." Id. at 134, 137. On October 17, 2017, Petitioner was seen by Dr. Alice De-Ling

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[25] IVIG is "used in the treatment of primary immunodeficiency disorders and [ITP]." Immune Globulin Intravenous (Human), Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=78975 (last visited Dec. 27, 2022).

[26] Nplate is a trademark for romiplostim, which is defined as "a thrombopoietin receptor agonist used for treatment of [ITP]." Romiplostim, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=44074 (last visited Dec. 27, 2022); see also Nplate, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=34407 (last visited Dec. 27, 2022).

[27] Petitioner's medical records continued to include references to idiopathic thrombocytopenia purpura and/or ITP on the problem list and in other parts of the records. However, this visit appears to mark the earliest date that Dr. Kale used the specific diagnosis of "immune thrombocytopenia" without also referencing the alternative diagnosis of "thrombocytopenia due to recent upper respiratory tract infection."

Ma, a hematologist at UNC Healthcare, "for a second opinion regarding therapy for chronic ITP." Pet. Ex. 6 at 8. Dr. Ma recommended either a splenectomy or Rituxan. Id. at 9. On October 19, 2017, Petitioner returned to Dr. Kale and discussed similar treatment options. Pet. Ex. 4 at 146. Petitioner decided she wanted to switch to Promacta[28] with Nplate as a backup if her platelet count dropped below 50,000. Id.

Petitioner's diagnosis was confirmed as chronic ITP on November 16, 2017. Pet. Ex. 4 at 148. She began taking Promacta and was seen for various follow ups from November 2017 throughout 2018. Id. at 160-61, 169, 179, 183, 188, 191, 197, 200, 209, 215, 218, 224, 227. At her December 7, 2018 follow up, her platelet count dropped to 39,000. Id. at 237. Dr. Kale increased Petitioner's Promacta dosage from 25 mg to 50 mg per day. Id.

Petitioner's platelet count increased on December 19, 2018 to 248,000 on 50 mg Promacta per day. Pet. Ex. 4 at 248. Dr. Kale switched her to alternating 25 mg and 50 mg every other day, and her platelet count on January 11, 2019 was stable at 75,000. Id. at 248-49. Petitioner mentioned she had gone to urgent care because she was having difficulty breathing, and she had been prescribed 60 mg of Prednisone. Id. at 244; Pet. Ex. 7 at 6-8. However, Petitioner claimed she had stopped taking the Prednisone prescribed during this appointment three weeks ago. Pet. Ex. 4 at 244. In February 2019, Petitioner's platelet count remained stable on the alternating doses of Promacta. Id. at 257.

Dr. Kale ordered another CT, which was conducted on April 5, 2019, to check on Petitioner's meningioma. Pet. Ex. 4 at 264. The CT showed no change since 2017. Id. at 264, 267. Petitioner began to taper her Promacta by taking 50 mg three days a week and 25 mg the other four days. Id. at 267. In June 2019, this was reduced to 50 mg twice a week and 25 mg five days a week. Id. at 277. Petitioner tolerated this well in August. Id. at 285; Pet. Ex. 11 at 9, 16. On October 9, 2019, Petitioner's platelets remained stable at 153,000, and Petitioner was directed to taper her Promacta to 25 mg every day. Pet. Ex. 11 at 25, 31. On December 6, 2019, Petitioner was clinically stable and her platelets were stable at 111,000. Id. at 39.

Dr. Ni Gorsuch, a hematologist, began seeing Petitioner on March 6, 2020, per the Petitioner's request. Pet. Ex. 14 at 19-37. Dr. Gorsuch and Petitioner discussed tapering off Promacta; however, Petitioner decided to stay on Promacta for the time being. Id. at 27. On June 4, 2020, Petitioner began the Promacta taper. Pet. Ex. 21 at 5. Petitioner discontinued Promacta on June 19, 2020. Id. at 15. On July 16, 2020, Petitioner's platelet count was 120,000 and Dr. Gorsuch noted Petitioner was stable without ITP relapse. Id. at 17-19. On October 19, 2020, Petitioner was seen by Dr. Gorsuch for a follow up. Id. at 23-31. Her ITP had not relapsed. Id. at 24. This remained true throughout 2021. Pet. Ex. 21 at 32-37; Pet. Ex. 24 at 5-9.

[28] Promacta, the trademark for eltrombopag olamine, "stimulates platelet production" and is "used for the treatment of thrombocytopenia in patients with chronic [ITP] who have had an insufficient response to other treatments." Eltrombopag Olamine, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=15982 (last visited Nov. 7, 2022); see also Promacta, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=41191 (last visited Dec. 27, 2022).

However, On January 11, 2022, Petitioner reported bruising and bleeding gums. Pet. Ex. 24 at 10. Her platelet count at this appointment was 110,000. Id. at 11.

No additional relevant medical records have been filed.

2. Petitioner's Affidavits[29]

Prior to the vaccination at issue, Petitioner "was healthy, active[,] and had no autoimmune diseases or hematological disorders, or any history of autoimmune disease or hematological disorders." Pet. Ex. 32 at ¶ 3. When Petitioner did get sick prior to the vaccination in 2016, she sought care from an urgent care and CVS minute clinic instead of a primary care physician. Id. at ¶¶ 6-7. In 2016, she began to establish care with permanent primary care and medical providers. Id. at ¶ 7. Petitioner reviewed her 2013 medical records that showed a slightly low platelet count. Id. at ¶ 12. She averred that at that time, she did not have symptoms of decreased platelets. Id. Further, she was not notified of the 137,000 count, nor was she instructed to return for follow up or seek treatment for this platelet count. Id.

Petitioner received her flu vaccine on October 9, 2016. Pet. Ex. 2 at ¶ 4. She started to notice bruising on the front and back of her thighs in mid-November 2016, around two weeks prior to her birthday on November 27, 2016. Id. at ¶¶ 10, 12. These bruises did not fade as ordinary bruises she had in the past did. Id. at ¶ 10.

On November 30, 2016, Petitioner began menstruating. Pet. Ex. 2 at ¶ 15. Petitioner's cycle lasted for 10 days instead of her normal four to five days and she felt dizzy, lightheaded, fatigued, and weak. Id. Petitioner continued to menstruate until December 9, 2016. Id.

On December 5, 2016, Petitioner developed a stuffy nose and other cold-like symptoms. Pet. Ex. 2 at ¶ 16. She continued to experience "spontaneous bruising, dizziness, lightheadedness, fatigue, weakness, and heavy menstruation[]." Id. The next day, Petitioner made an appointment to see her OB/GYN. Id. at ¶ 17. On December 7, 2016, Petitioner visited her OB/GYN where she underwent a full panel of blood work, and she was prescribed a Z-pak for her stuffy nose. Id. at ¶ 18. On December 8, 2016, Petitioner's physician notified her that her "platelets were critically low at 12,000 and that [she] needed to see a hematologist as soon as possible." Id. at ¶ 19.

Dr. Kale saw Petitioner on December 12, 2016. Pet. Ex. 2 at ¶ 21. At this appointment, she was diagnosed with ITP and was prescribed 60 mg of prednisone. Id. Petitioner's platelet count increased to 126,000 the following week and she began a prednisone taper. Id. at ¶ 22.

Petitioner returned for a follow up visit on December 27, 2016. Pet. Ex. 2 at ¶ 23. Her platelet count had dropped to 32,000. Id. She restarted prednisone and her platelet count increased. Id. Dr. Kale advised her she had ITP that was responsive to steroids and steroid

[29] Petitioner submitted two affidavits executed on September 24, 2019 and March 3, 2022. Pet. Exs. 2, 32. The second affidavit was not notarized.

dependent. Id. In January 2017, Petitioner switched to Rituxan therapy and began to taper her prednisone. Id. at ¶ 24. Petitioner's platelets increased by early February 2017. Id.

Following a nosebleed, Petitioner returned to Dr. Kale's office on February 12, 2017. Pet. Ex. 2 at ¶ 25. Her platelet count had dropped to 9,000. Id. She immediately reported to the hospital for possible IVIG treatment. Id. She was admitted to the hospital on February 14, 2017, where she received two doses of IVIG and Nplate treatments. Id. at ¶ 26. She was discharged the following day. Id. By March 2017, her platelets increased to 191,000 and she remained on 20 mg of prednisone. Id. Between March 2017 and October 2017, Petitioner was consistently on prednisone and receiving weekly Nplate shots. Id. at ¶ 27. Her platelets fluctuated greatly over this period. Id.

Petitioner saw Dr. Ma at UNC Healthcare on October 17, 2017 for a second opinion. Pet. Ex. 2 at ¶ 28. Dr. Ma suggested Cellcept, Promacta, or a splenectomy as alternative courses of treatment. Id. She recommended repeating Rituxan if the splenectomy failed. Id. However, since Petitioner was on Nplate successfully, Dr. Ma recommended staying on Nplate or switching to Promacta. Id.

From October 2017 to November 2017, Petitioner continued to take prednisone and receive weekly Nplate shots. Pet. Ex. 2 at ¶ 29. On November 16, 2017, Petitioner began taking Promacta at 25 mg per day. Id. She remained on Promacta, taking 25 mg every day except Mondays and Fridays, when she took 50 mg. Id. at ¶ 30.

Petitioner weaned off Promacta in June 2020. Pet. Ex. 32 at ¶ 14. She follows up with her hematologist once a year and has her platelets checked twice a year when she sees her hematologist and when she gets her yearly physical. Id. Her platelets remain lower than normal; however, they are stable enough for her to feel comfortable. Id.

Petitioner explained how her diagnosis has affected her emotionally, physically, and psychologically. Pet. Ex. 2 at ¶ 31. She described that

> [p]hysical activity is harder now. The long list of medications and treatments [she has] been on have been very hard on [her] body. The steroids (prednisone and dexamethasone) have made [her] shoulders, hips, and knees ache. They have also caused significant weight gain and [she is] very sensitive to heat now and overheat[s] easily. This limits [her] from being able to go outside or do things with [her] daughter a lot during the hot summer months. [Her] moods are affected, and [she has] a lot of mood swings. [She] also ha[s] extreme fatigue. [She] ha[s] talked to [her] doctor about this, especially insomnia.

Id.

When Petitioner's counts are lower, she must be extremely careful. Pet. Ex. 2 at ¶ 32. She explained that her social life has been affected by her diagnosis. Id. at ¶ 33. She constantly worries during her menstrual cycle every month. Id. She looks for bruises and blood blisters and worries she will catch something during cold/flu season that would cause her platelets to

decrease. Id. Petitioner also claims her diagnosis has also impacted her ability to work. Id. at ¶ 34. She cannot work more than part time due to her extreme fatigue that results from her medications. Id. Petitioner also suffered financially due to her diagnosis. Id. at ¶ 35.

D. Expert Reports

1. Petitioner's Expert, Dr. Abhimanyu Ghose[30]

a. Background and Qualifications

Dr. Ghose is a medical doctor board certified in hematology, oncology, and internal medicine. Pet. Ex. 15 at 3; Pet. Ex. 16 at 1. After receiving his M.B.B.S. in 2007 from Nilratan Sircar Medical College in India, he worked in India as a physician before beginning a residency in 2009 at the University of Toledo, Ohio and completed a fellowship in hematology oncology in 2015. Pet. Ex. 15 at 2; Pet. Ex. 16 at 2. He currently sees patients and conducts clinical research at Arizona Oncology/US Oncology Network. Pet. Ex. 15 at 3; Pet. Ex. 16 at 1. In addition, he is a clinical research professor of Internal Medicine, Hematology Oncology at A.T. Still University School of Osteopathic Medicine in Arizona. Pet. Ex. 16 at 1. Prior to this appointment, he held various hematology and oncology positions and has been an expert witness since 2019. Id. at 1-2. He is a member of and has served on various societies and boards focused on hematology and oncology. Id. at 8. Dr. Ghose has also authored or co-authored over 30 publications, abstracts, and presentations. Id. at 3-6. Dr. Ghose sees patients with ITP on a regular basis. Pet. Ex. 15 at 3.

b. Opinion

i. Althen Prong One

Dr. Ghose opined that molecular mimicry is the causal mechanism that triggers autoimmunity by the flu vaccination. Pet. Ex. 15 at 11. Specifically, antibodies against the antigens in the vaccine cross-react with normal platelet antigens in the host. Id. at 8. In support of his opinion, Dr. Ghose cited Perricone et al., in which the authors state that molecular mimicry is the "most likely" theory by which vaccines induce ITP. Pet. Ex. 17(e) at 1. Molecular mimicry describes the process in which "[a]ntibodies responsible for the clearance of virus antigens may cross-react with antigens naturally present on platelets." Id. at 2. While this is the current prevailing theory, the pathogenic mechanisms of ITP have not been fully explained. Id.

In addition to Perricone et al., Dr. Ghose cited other supportive literature about molecular mimicry. For example, in Cecinati et al.,[31] the authors conducted a literature review of ITP following vaccine administration. Pet. Ex. 17(p) at 1. They explained that ITP "following vaccine administration depends on the development of autoantibodies that cross-react with the

[30] Dr. Ghose provided one expert report. Pet. Ex. 15.

[31] Valerio Cecinati et al., Vaccine Administration and the Development of Immune Thrombocytopenic Purpura in Children, 9 Hum. Vaccines & Immunotherapeutics 1158 (2013).

naturally present antigenic targets on platelets," or molecular mimicry. Id. A "defective immune regulation" caused by genetic abnormality also "may play a role in the pathogenesis of the disease." Id. at 2.

The authors in Cecinati et al. focused on the association between MMR and ITP. Pet. Ex. 17(p) at 1-2. They noted that "[v]accine-related thrombocytopenia is considered to be of immune origin because antibodies can be detected on platelets in about 79% of cases." Id. at 1. Based on data from surveillance systems, they reported that cases of ITP following vaccination are generally infrequent and less severe. Id. at 2. The authors also noted that the "[t]rivalent inactivated [flu] vaccine (TIV) has been associated with ITP in a very small number of adult case reports," as well as a surveillance study by Garbe et al.[32] Id. at 3; see Pet. Ex. 17(f).

Dr. Ghose relied on papers that show an association between ITP and MMR vaccinations, as well as a variety of other vaccines, including diphtheria-tetanus-pertussis ("DTP"), hepatitis A, varicella, and flu. Pet. Ex. 15 at 10. One of these was authored by Rinaldi et al., which provided a review of bacteria, viruses, and vaccines associated with ITP. Pet. Ex. 17(d) at 1. The authors postulated that the association between vaccinations and ITP is similar to that between infections and ITP, and they identified molecular mimicry as the likely mechanism. Id. at 8.

The first example of a study cited by Dr. Ghose reporting an association between the MMR vaccine and ITP is a case-control study performed by Black et al. Pet. Ex. 17(q) at 1. This study used the United Kingdom ("UK") General Practice Research Database[33] to identify children who were diagnosed with ITP between January 1988 and December 1999. Id. at 1-2. The authors identified all children who developed ITP within six weeks of receiving an MMR vaccine, where another cause was not identified, as "'possible vaccine-related' cases." Id. at 2. Out of the 63 cases, 52 received an MMR vaccination before their date of ITP diagnosis. Id. Of the 23 children between 13 and 24 months of age, eight developed ITP within six weeks of receiving their first MMR vaccine. Id. at 3, 3 tbl.2. Based on their data, the authors concluded there was a six-fold increase in the risk of ITP in children 13 to 24 months old during the six weeks post-MMR vaccination. Id. at 4.

Another study reporting a causal association between the MMR vaccination and ITP was by Miller et al. who studied UK immunization and hospital records between 1991 and 1994. Pet. Ex. 17(c) at 1. The authors reviewed immunization records and hospital records for children admitted to the hospital with ITP and found 28 admissions for ITP in 21 children with a prior

[32] Edeltraut Garbe et al., Drug-Induced Immune Thrombocytopaenia: Results from the Berlin Case-Control Surveillance Study, 68 Eur. J. Clinical Pharmacology 821 (2012). This article is also cited by Petitioner's other expert. Pet. Ex. 20(s).

[33] The UK General Practice Research Database collects "[s]tandardized sets of information" from "500 practices throughout the UK." D. H. Lawson et al., The General Practice Research Database: Scientific and Ethical Advisory Group, 91 Q. J. Med. 445, 445 (1998). The Office for National Statistics ("ONS") maintains and runs the "information resource on behalf of the Department of Health." Id.

MMR vaccination. Id. The "study confirm[ed] a casual association between MMR vaccine and ITP." Id. at 2.

Next, Dr. Ghose offered studies about the association between the flu vaccine and ITP. Pet. Ex. 15 at 10-11. He cited a large case-control surveillance study by Garbe et al., who used data from Berlin hospitals on adults from 2000 to 2009. Pet. Ex. 17(f) at 1. Ninety of the 169 total cases of ITP were determined to be drug-related, and these included vaccines.[34] Id. at 1-2, 9. Three of the vaccine cases were related to the flu vaccine. Id. Vaccine causality was determined to be "probable" using the World Health Organization ("WHO") standardized causality assessment tool.[35] Id. at 9. The "[flu] vaccination was associated with a statistically significant [four]-fold risk." Id.

Jadavji et al.[36] reported on data obtained from 12 pediatric centers in Canada from 1992 to 2001. Pet. Ex. 17(l) at 1. The authors identified 61 patients who had decreased platelet counts ($< 50 \times 10^9$/l) within 30 days of vaccination. Id. Two of the patients developed thrombocytopenia after the flu vaccine.[37] Id. at 2.

Dr. Ghose also cited a number of case reports of ITP following flu vaccination. Pet. Ex. 15 at 10-11. Casoli and Tumiati[38] reported a case of acute ITP that "presented with sudden onset of petechiae and ecchymoses, as possible complication of antiinfluenza vaccination with

[34] Since the Garbe et al. study was conducted on adults, there were no cases of ITP related to the MMR vaccination. See Pet. Ex. 17(f) at 9.

[35] The WHO assessment of causality includes the categories certain, probable, possible, unlikely, unclassified, and unclassifiable. Pet. Ex. 17(f) at 3. "A drug reaction was evaluated as 'probable' when the ITP occurred with a reasonable time [after] administration[,] . . . was unlikely to be attributed to other causes, and a positive dechallenge reaction was observed on drug withdrawal." Id. at 3-4.

[36] Taj Jadavji, et al., Thrombocytopenia After Immunization of Canadian Children, 1992 to 2001, 22 Pediatric Infectious Disease J. 119 (2003).

[37] Of note, the authors noted a limitation of the study, in that the majority of patients with post-vaccination thrombocytopenia also had a viral infection or exposure to medication that could suggest an alternate cause of the illness. Pet. Ex. 17(l) at 3.

[38] P. Casoli & B. Tumiati, Acute Idiopathic Thrombocytopenic Purpura After Anti-Influenza Vaccination, 9 Medicina (Firenze) 417 (1989). Only the abstract of this article was filed as the article was in Italian.

inactivated viruses" administered 15 days prior to onset. Pet. Ex. 17(i) at 1. Tsuji et al.[39] reported the case of a 79-year-old who developed thrombocytopenia four days after receiving a flu vaccine. Pet. Ex. 17(j) at 1. Nagasaki et al.[40] reported ITP following flu vaccination in three elderly patients, ages 75, 81, and 87. Pet. Ex. 17(g) at 1-2. The authors concluded that "[v]accine-associated ITP [was] probably caused by molecular mimicry." Id. at 2. They also concluded that ITP was "strongly suspected" to be associated with the flu vaccine. Id. at 4.

Tishler et al.[41] reported on a 68-year-old patient who developed severe thrombocytopenia 14 days following receipt of a flu vaccine. Pet. Ex. 17(h) at 1. Regarding causation, the authors explained that "[t]he most popular hypothetical mechanism for the triggering of autoimmunity by an infectious agent is that of molecular mimicry." Id.

Shalmovitz and Johar[42] described a 50-year-old man who developed Evans' syndrome, which is the combination of ITP and autoimmune hemolytic anemia with no known underlying cause. Pet. Ex. 17(k) at 1. The patient had received a flu vaccine four days before his onset of symptoms. Id. The authors postulated that the flu vaccine, through molecular mimicry, may have been the cause of the patients Evans' syndrome. Id. at 2. The authors performed a PubMed[43] search and came across eight case reports of patients who developed ITP after receiving a flu vaccine. Id. The authors opined that these case reports "suggest that immunizations may provide a trigger for the development of autoimmune disease in susceptible individuals." Id.

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[39] Takahiro Tsuji et al., Refractory Idiopathic Thrombocytopenic Purpura Following Influenza Vaccination, 50 Rinsho Ketsueki 577 (2009). Again, only the abstract of this article was filed as the article was originally in Japanese. This article is also cited by Petitioner's other expert. Pet. Ex. 20(x).

[40] Joji Nagasaki et al., Postinfluenza Vaccination Idiopathic Thrombocytopenic Purpura in Three Elderly Patients, 2016 Case Reps. Hematology 1. This article is also cited by Petitioner's other expert. Pet. Ex. 20(z).

[41] Moshe Tishler et al., Immune Thrombocytopenic Purpura Following Influenza Vaccination, 8 Isr. Vaccine Rsch. Initiative 322 (2006).

[42] Gil Z. Shlamovitz, & Sandeep Johar, A Case of Evans' Syndrome Following Influenza Vaccine, 44 J. Emergency Med. e149 (2013). This article is also cited by Petitioner's other expert. Pet. Ex. 20(p).

[43] "PubMed is a free resource supporting the search and retrieval of biomedical and life sciences literature . . . . The PubMed database contains more than 34 million citations and abstracts of biomedical literature." Nat'l Libr. Med., Nat'l Ctr. for Biotechnology Info., PubMed Overview, https://pubmed.ncbi.nlm.nih.gov/about/ (last visited Nov. 9, 2022).

And Mantadakis et al.[44] described a case report of a 3-year-old boy who developed ITP 26 days after his second dose of the flu vaccine. Pet. Ex. 17(o) at 1. The researchers postulated that the mechanism of thrombocytopenia following flu infection was most likely due to molecular mimicry. Id. at 2. The authors concluded that while there was a risk of ITP six to eight weeks following the MMR vaccine, more evidence was needed to explore the connection between the flu vaccine and ITP. Id. at 2-3.

Lastly, Dr. Ghose cited two cases where immunosuppressed patients developed ITP following flu vaccination. The first of these cases was reported in a letter authored by Ikegame et al.[45] about a bone marrow transplant recipient whose platelet count rapidly decreased two weeks after receiving a flu vaccine. Pet. Ex. 17(m) at 1-2. At the time of vaccination, the patient was receiving low doses of tracrolimus (1.7 mg/day) and prednisone (7 mg/day). Id. at 1. The authors suggested that the causal theory was molecular mimicry, stating "[a]cute ITP may [] occur after vaccination" because "[a]ntibodies responsible for the clearance of virus antigens may cross-react with antigens naturally present on platelets." Id. at 2.

The second case report involving an immunosuppressed patient was authored by Mamori et al.[46] and described a 75-year-old patient with autoimmune liver disease ("AILD") who received a flu vaccine. Pet. Ex. 17(n) at 1. One week after vaccination, the patient began experiencing symptoms and was diagnosed with ITP. Id. The authors concluded that "the [flu] vaccine can exacerbate potential immune-mediated platelet destruction in AILD patients, thus leading to severe autoimmune side effects." Id. at 2.

ii. Althen Prongs Two and Three

Dr. Ghose opined ITP usually develops within four to 35 days following flu vaccination. Pet. Ex. 15 at 12. Petitioner was vaccinated on October 9, 2016. Id.; see also Pet. Ex. 1 at 3; Joint Submission at 1. Dr. Ghose opined Petitioner's symptoms began in mid-November "when she developed bruises on her thighs the size of a quarter." Pet. Ex. 15 at 12. Dr. Ghose explained this "[e]asy bruising is a classic sign of ITP." Id. This would place Petitioner's symptom onset around 35 days after her vaccination, which is within Dr. Ghose's proposed time frame of 4-35 days. Id.

In support of his opinion as to the appropriate temporal association, Dr. Ghose cited Cecinati et al. The authors performed a review of the available literature regarding ITP following vaccine administration and concluded that "vaccine-related ITP usually occurs within six weeks of vaccination." Pet. Ex. 17(p) at 2.

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[44] Elpis Mantadakis et al., A Case of Immune Thrombocytopenic Purpura After Influenza Vaccination: Consequence or Coincidence?, 32 J. Pediatric Hematology Oncology E227 (2010).

[45] K. Ikegame et al., Idiopathic Thrombocytopenic Purpura After Influenza Vaccination in a Bone Marrow Transplantation Recipient, 38 Bone Marrow Transplantation 323 (2006).

[46] Satoshi Mamori et al., Thrombocytopenic Purpura After the Administration of an Influenza Vaccine in a Patient with Autoimmune Liver Disease, 77 Digestion 159 (2008).

Dr. Ghose also cited several case reports to support his timeline of temporal association. In Nagasaki et al., three patients were diagnosed with thrombocytopenia following flu vaccinations. Pet. Ex. 17(g) at 1-2. These patients began experiencing symptoms two weeks, four weeks, and five weeks following flu vaccination. Id. In Tishler et al., the authors reported a 68-year-old patient who developed severe thrombocytopenia 14 days after a flu vaccine. Pet. Ex. 17(h) at 1. Casoli and Tumiati described a patient who developed ITP within 15 days of anti-flu vaccination. Pet. Ex. 17(i) at 1. In the Mantadakis et al. case report, the three-year-old patient developed ITP 26 days following "a second dose of immunization against seasonal [flu]." Pet. Ex. 17(o) at 1.

Dr. Ghose found the time between vaccination and onset of symptoms to demonstrate an appropriate temporal association in this case. Pet. Ex. 15 at 12. He determined the time between Petitioner's vaccination and onset of symptoms to be roughly 35 days in mid-November. Id. He cited several case reports demonstrating an appropriate onset timeline to be within seven days to six weeks. Id. Therefore, he opined that Petitioner's ITP was temporally associated with her flu vaccine. Id.

Lastly, Dr. Ghose concluded that "[t]he only event that led to [Petitioner's] disease and suffering was the [flu] vaccine." Pet. Ex. 15 at 13.

2. Petitioner's Expert, Dr. Marc Serota[47]

a. Background and Qualifications

Dr. Serota currently works as an attending physician at the Veteran's Affairs Hospital in Denver and as a supervising physician in dermatology at the University of Colorado. Pet. Ex. 19 at 1-2. He is board certified in pediatrics, allergy/immunology, and dermatology. Pet. Ex. 18 at 1; Pet. Ex. 19 at 1, 3. He received his B.A. and M.D. from the University of Missouri, Kansas City in 2007. Pet. Ex. 19 at 1. Thereafter, he completed a pediatrics residency at Cohen's Children's Hospital in New York, an allergy/immunology fellowship at Children's Mercy Hospital in Kansas City, Missouri, and a dermatology residency at the University of Colorado, Denver. Id. Dr. Serota has authored or co-authored over 10 peer reviewed articles and abstracts and has presented at over 25 lectures and professional conferences. Id. at 3-5.

b. Opinion

i. Althen Prong One

Dr. Serota defined ITP as "an acquired thrombocytopenia caused by autoantibodies against platelet antigens." Pet. Ex. 18 at 2 (quoting Pet. Ex. 20(aa) at 1). He explained that viral infections, and less often bacterial infections, can trigger ITP. Id. at 3. In support of these general propositions, Dr. Serota cited Cooper and Bussel, who stated that ITP probably occurs due to a "combination of genetic susceptibility and environmental factors," including viral

[47] Dr. Serota provided one expert report. Pet. Ex. 18.

infection. Id. at 5 (quoting Pet. Ex. 33 at 6). The authors suggested that viral infections can initiate ITP through the mechanism of molecular mimicry. Id. (citing Pet. Ex. 33 at 6).

Dr. Serota opined that molecular mimicry is thought to be the mechanism that explains how viral infections and drugs can cause ITP. Pet. Ex. 18 at 4. He cited an article by Perera and Garrido[48] that describes the complex mechanism of ITP triggered by molecular mimicry. Pet. Ex. 20(m) at 1. Perera and Garrido wrote "immune thrombocytopenia (ITP) was thought to be caused by the destruction and insufficient production of platelets, as mediated by autoantibodies." Id.

> The trigger may be a loss of tolerance due to molecular mimicry with cross-reaction of antibodies arising from infectious agents or drugs, genetic factors, and/or platelet Toll receptors. This loss of tolerance activates autoreactive effector B and T lymphocytes, which in turn initiates platelet destruction, mediated by cytotoxic T lymphocytes and the release of pro-inflammatory cytokines (IL-2/IL-17) by T helper (Th) cells (Th1/Th17). Th2 (antiinflammatory) and regulatory B (Breg) and Treg cells are also inhibited (with decrease in IL-10/TGF-β), which leads to the disease becoming chronic. Some isotypes of autoantibodies may increase the bleeding risk. Corticosteroids, rituximab, and thrombopoietin receptor agonists (A-TPOs) all increase levels of Tregs and TGF-β. The A-TPOs also increase Breg levels, which could explain why complete remission has been seen in some cases.

Id.

Regarding infectious causes, Dr. Serota cited several case studies to demonstrate that an influenza infection can cause ITP. Pet. Ex. 18 at 5. For example, Lee et al.[49] reported a patient with the 2009 H1N1 flu A virus who developed acute ITP and leukopenia on the third day of his viral illness. Pet. Ex. 20(i) at 2-3. The authors noted that typical ITP develops two to three weeks following vaccination; however, in the this reported case, ITP occurred during viral infection. Id. at 3. The authors found this distinction and the mechanism of flu-associated ITP is not fully understood. Id.

After discussing the relationship between flu infection and ITP, Dr. Serota moved to the flu vaccine and its causal role in ITP. Pet. Ex. 18 at 6-9. He cited many of the same studies and case reports cited by Dr. Ghose, described above, including those authored by Garbe et al., Nagasaki et al., Tsuji et al., and Shlamovitz and Johar. Pet. Exs. 17(f), 17(g), 17(j), 17(k). A discussion of these articles will not be repeated here.

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[48] María Perera & Teresa Garrido, Advances in the Pathophysiology of Primary Immune Thrombocytopenia, 22 Hematology 41 (2017).

[49] Chun-Yi Lee et al., Acute Immune Thrombocytopenic Purpura in an Adolescent with 2009 novel H1N1 Influenza A Virus Infection, 74 J. Chinese Med. Ass'n 425 (2011).

Dr. Serota also cited many papers that referenced molecular mimicry as the relevant causal theory. For example, Isai et al.[50] reviewed a database of reports of suspected adverse reactions in the European Union from October 2009 to December 2010 for adjuvanted and non-adjuvanted pandemic flu A/H1N1 vaccines. Pet. Ex. 20(n) at 1. The data included reports of autoimmune adverse reactions where an adjuvanted or unadjuvanted A/H1N1 vaccine was reported as suspect, interacting, or concomitant. Id. at 2. The authors reported that ITP was the third most common autoimmune condition following flu vaccination. Id. at 3 tbl.2. David and Shoenfeld[51] found "vaccines could lead to ITP by molecular mimicry" when "[c]onsidering the pathogenesis of autoimmune disorders following infections." Pet. Ex. 20(o) at 1.

Perhaps the most compelling evidence of causation are the case reports referenced by Dr. Serota, authored by Hamiel et al.[52] and Almohammadi et al.,[53] that discuss patients with recurrent episodes of ITP following administration of the flu vaccination. Pet. Ex. 20(r) at 1; Pet. Ex. 20(t) at 1.

Hamiel et al. described a four-and-one-half-year-old boy who presented in October 2013 with bleeding. Pet. Ex. 20(r) at 1. His platelet count was severely decreased at 17,000. Id. A review of the child's past medical records revealed that he had previously been hospitalized at age one-and-one-half years and three-and-one-half years of age with similar symptoms of bleeding. Id. at 2. All three of the child's hospital admissions for ITP had taken place within one week of his receipt of the flu vaccine. Id. And all three times the child received the Fluarix trivalent flu vaccine. Id. After the last occurrence, the child did not receive any further annual flu vaccines, and no recurrences of ITP were observed. Id. Using the WHO standardized case causality assessment, the flu vaccine was determined to fall into the category of "certain" causality. Id.

Almohammadi et al. described an adult who presented with epistaxis, gross hematuria, and bleeding gums two days after receiving flu and pneumococcal conjugate vaccines. Pet. Ex. 20(t) at 1. The patient reported that he had experienced epistaxis after receipt of the flu vaccination for the prior three years. Id. The authors concluded that it was "highly likely" that the patient's severe thrombocytopenia was "due to the [flu] vaccination" because of the temporal association, lack of other causes, and history of only having epistaxis after prior flu vaccinations. Id. at 2.

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[50] Alina Isai et al., Autoimmune Disorders After Immunisation with Influenza A/H1N1 Vaccines with and Without Adjuvant: EudraVigilance Data and Literature Review, 30 Vaccine 7123 (2012).

[51] Paula David & Yehuda Shoenfeld, ITP Following Vaccination, 99 Int'l J. Infectious Diseases 243 (2020).

[52] Uri Hamiel et al., Recurrent Immune Thrombocytopenia After Influenza Vaccination: A Case Report, 138 Pediatrics e1 (2016).

[53] Abdullah Almohammadi et al., Epistaxis and Gross Haematuria with Severe Thrombocytopaenia Associated with Influenza Vaccination, 12 BMJ Case Reps. 1 (2019).

ii. Althen Prongs Two and Three

Dr. Serota agreed with Petitioner's diagnosis of chronic ITP. Pet. Ex. 18 at 9. He opined that Petitioner's October 9, 2016 flu vaccine caused her ITP "to a reasonable degree of medical certainty." Id.

Dr. Serota disagreed with Respondent's contention that Petitioner's sinus infection or upper respiratory infection could have caused her ITP. Pet. Ex. 18 at 9. Dr. Serota opined that the onset of Petitioner's ITP symptoms began on November 13, 2016, 35 days after her flu vaccination. Id. at 1, 9. He based this date on the facts set forth in Petitioner's affidavit, where she began "to experience random and spontaneous bruising." Id. at 1. Petitioner's sinus infection or upper respiratory infection began December 5, 2016 based on Petitioner's affidavit. Id. Therefore, Dr. Serota opined that Petitioner developed her sinus infection or upper respiratory infection after the onset of her ITP. Id. at 9. Thus, Dr. Serota did not believe that there was any other likely cause of Petitioner's ITP, other than her flu vaccination. Id.

Dr. Serota cited studies that described the temporal association between ITP and vaccinations generally in support of his opinion that the timeframe of 35 days is appropriate given the mechanism of molecular mimicry. Pet. Ex. 18 at 7-9. Black et al. identified an increased risk of developing ITP six weeks after vaccination. Pet. Ex. 17(q) at 1. Dr. Serota explained that "[a]n autoimmune response to a stimulus does not occur immediately and frequently takes between 10-60 days (depending on the particular nature and mechanisms of the immunologic response) to develop." Pet. Ex. 18 at 9. He continued, "[t]his timeframe is in keeping with the published literature involving the development of ITP in similar vaccine related cases." Id.

In conclusion, Dr. Serota opined, "to a reasonable degree of medical certainty, that [Petitioner] developed chronic ITP as a result of the antigenic exposure to the [flu] vaccine she received on [October 9, 2016]." Pet. Ex. 18 at 9.

3. Respondent's Expert, Dr. Lisa Baumann Kreuziger[54]

a. Background and Qualifications

Dr. Baumann Kreuziger is board certified in hematology and oncology. Resp. Ex. A at 1; Resp. Ex. B at 2. She graduated from the University of Wisconsin-Madison, School of Medicine and Public Health in 2006 and thereafter completed her internal medicine residency at the Mayo Clinic and a fellowship at the University of Minnesota. Resp. Ex. B at 1. Dr. Baumann Kreuziger currently holds various faculty, administrative, and hospital staff appointments. Id. at 2. She has been invited to lecture at over 40 functions and has worked on over 20 peer reviewed workshops and presentations. Id. at 5-10. Dr. Baumann Kreuziger has authored or co-authored over 50 publications. Id. at 15-19.

[54] Dr. Baumann Kreuziger provided one expert report. Resp. Ex. A.

b. Opinion

i. Althen Prong One

Dr. Baumann Kreuziger agreed that both genetic and environmental risk factors can contribute to ITP. Resp. Ex. A at 4. Specific infections including *H. pylori*, hepatitis C, HIV, cytomegalovirus, and EBV have been associated with ITP. Id. She also agreed that "[m]olecular mimicry between viral infections, especially between the hepatitis C and HIV molecules has been shown." Id. (internal citations omitted). However, Dr. Baumann Kreuziger did not agree that there is a causal association between the flu vaccine and ITP, or that molecular mimicry was an appropriate mechanism to explain any purported relationship. Id. at 4-5.

Instead of molecular mimicry, Dr. Baumann Kreuziger suggested that "[m]echanistic studies have shown that platelets treated with [flu] virus undergo lysis, or bursting, by the classical complement pathway." Resp. Ex. A at 4. Further, she opined that viral replication of the viral protein, hemagglutinin ("HA"), is necessary to trigger the mechanism for a virus to cause ITP. Id. Because the flu vaccine is a killed virus, she stated that it does not undergo viral replication, and viral HA is not present, and therefore not able to trigger the molecular mimicry necessary to cause ITP. Id.

In support of this opinion, she cited a study published in 1984 by Kazatchkine et al.[55] Resp. Ex. A at 4 (citing Resp. Ex. E). This study showed that "incubation of human platelets with suspensions of [flu] virus, but not with bacterial neuraminidase, results in complement and antibody-mediated lysis of platelets in autologous serum. The crucial event was the interaction of immunoglobulins with viral [HA] present on the platelet membrane." Resp Ex. E at 1-2. This "[b]inding of a viral protein to the platelet surface provides a model for immune thrombocytopenias occurring during acute viral infections at the time of the specific immune response." Id. at 1. Platelets not treated with virus were also exposed to antibodies, but lysis did not occur in these cells, suggesting the binding of viral HA was necessary. Id. at 4-5.

Although she rejected Petitioner's proffered theory of molecular mimicry, Dr. Baumann Kreuziger cited articles acknowledging the mechanism and its causal role in ITP. Swinkels et al. stated that molecular mimicry is "[o]ne of the suggested mechanisms by which infections lead to autoimmunity." Resp. Ex. K at 3. "[C]ross reactivity may occur against platelet receptors, which subsequently lead to autoantibodies specific for both the viral protein and platelet receptors."[56] Id.

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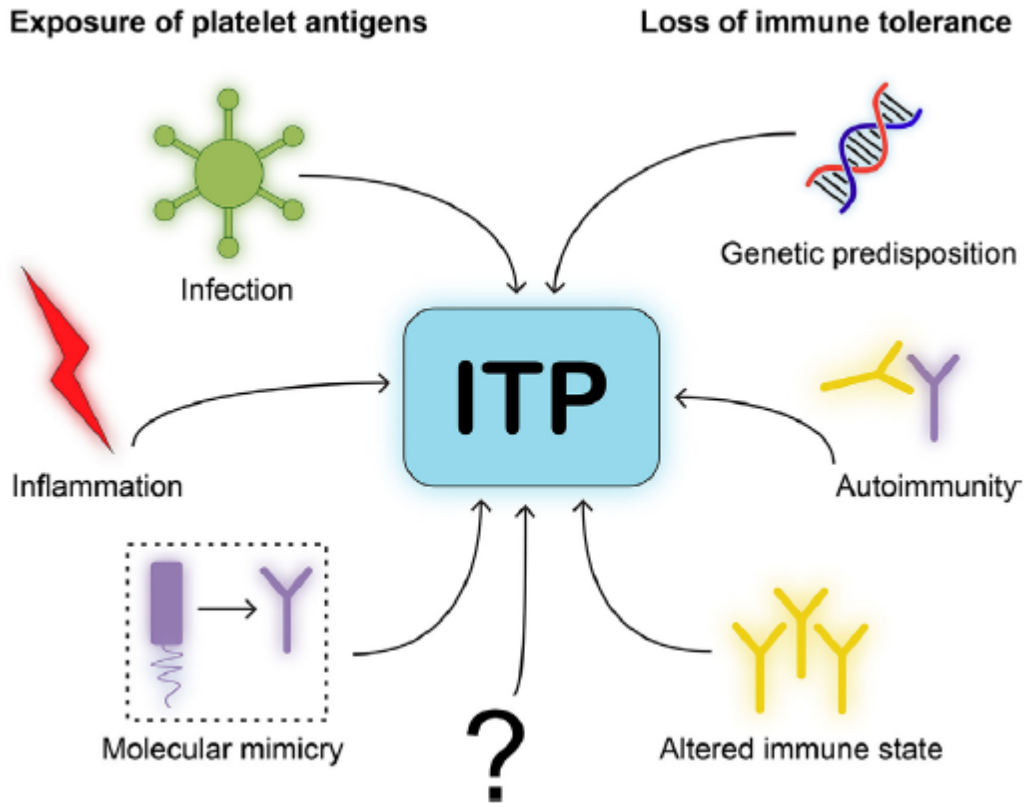
[55] Michel D. Kazatchkine et al., Membrane-Bound Hemagglutinin Mediates Antibody and Complement-Dependent Lysis of Influenza Virus-Treated Human Platelets in Autologous Serum, 74 J. Clinical Investigation 976 (1984).

[56] For a more detailed discussion of the mechanisms at play in the etiology ITP, see Resp. Ex. K at 3-8.

Swinkels et al. proposed a "simplified" model for immune thrombocytopenia, or ITP, illustrated below.



Resp. Ex. K at 8 fig.3. This model contemplates a trigger in one who has a genetic predisposition, and a causal theory of molecular mimicry between viral antigens and platelet glycoproteins. See id. Additionally, there is a loss of immune tolerance, due to a genetic predisposition or altered immune state. See id.

Dr. Baumann Kreuziger also dismissed the case reports cited by Petitioner's experts, stating, "[c]ase reports only provide information that an outcome such as an autoimmune disease occurred after an event such as [flu] immunization. Case reports are highly prone to publication bias." Resp. Ex. A at 4-5. She cited a study authored by Albrecht et al.[57] that evaluated case reports and case series published in *The Lancet* from January 1996 to June 1997 and found "a strong publication bias favoring positive results" as well as the need for the "opportunity . . . for publication of follow-up reports." Resp. Ex. C at 1. Albrecht et al., however, did not look at adverse effects of vaccines but instead focused on "[i]nnovative or unusual treatment" and outcomes. Id. at 2. Thus, their findings do not appear particularly relevant. Importantly, the authors acknowledged the value of case reports, stating that "[f]requently, discovery of therapeutic advances in medicine happens only serendipitously through unanticipated side effects; therefore, case reports and series remain a cornerstone of medical progress." Id. at 1.

[57] Joerg Albrecht et al., Case Reports and Case Series from *Lancet* Had Significant Impact on Medical Literature, 58 J. Clinical Epidemiology 1227 (2005).

Instead of case reports, Dr. Baumann Kreuziger referenced case control and large cohort studies, which she believes to be more reliable. Resp. Ex. A at 5. She acknowledged that Garbe et al., cited by Petitioner's experts, reported an increased risk of ITP following flu vaccination. Id. (citing Pet. Ex. 17(f) at 7). She opined, however, that there was not a "preponderance of the medical literature" reporting an association between the flu vaccination and ITP. Id.

Dr. Baumann Kreuziger cited a self-controlled case series from Hur et al.,[58] in which the authors analyzed 2.1 million adult Veterans who received flu vaccines between October 1, 2010, and March 31, 2011. Resp. Ex. F at 1. The study found "[n]o significant risks" for ITP, Guillain-Barré Syndrome ("GBS"), or Bell's palsy following the 2010-2011 flu vaccine.[59] Id.

Another study cited by Dr. Baumann Kreuziger was from Grimaldi-Bensouda et al.,[60] which studied adults diagnosed with ITP from April 2008 to June 2011. Resp. Ex. D at 1. They compared 198 patients with ITP from internal medicine and hematology centers in France with 878 controls and found no association between vaccinations, including the flu vaccine, and ITP, using a 12-month window. Id. Using a two-month window, the authors found an increased risk of ITP, "mainly attributable to vaccination against diphtheria-tetanus-pertussis-poliomyelitis;" however, the increase was not statistically significant. Id. Notably, of the 198 patients with ITP, the majority had not received the flu vaccine (no exposure within 12 months, 154 or 77.8%) and 187 (94.4%) had not been exposed to the flu vaccine within two months. Id. at 5 tbl.3. Because the study population had limited exposure to the flu vaccine, it is not clear whether the results are applicable to the facts of this case.

Two other studies cited by Dr. Baumann Kreuziger do not support her opinions because the flu vaccine may not have been administered to the study participants. The first was a study by Sauvé et al.[61] Resp. Ex. I. Dr. Baumann Kreuziger stated that it was "a study of 107 cases of post-vaccination ITP from Canada, [and] none of the cases had received a[] [flu] vaccine." Resp. Ex. A at 5 (citing Resp. Ex. I at 1-2, 2 tb.1). The study reviewed pediatric data from 1992 to 2002 and included patients who received the MMR, DTP/DTaP, meningococcus C, and varicella vaccines. Resp. Ex. I at 2 tbl.1. It does not appear, however, that the children in the study received the flu vaccine. See id.

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[58] Kwan Hur et al., Safety of the 2010-2011 Influenza Vaccinations in the Department of Veteran Affairs, 28 Pharmacoepidemiology & Drug Safety 361 (2012).

[59] Only the abstract of this study was filed, and therefore, it is difficult to provide a meaningful analysis of it.

[60] Lamiae Grimaldi-Bensouda et al., A Case-Control Study to Assess the Risk of Immune Thrombocytopenia Associated with Vaccines, 120 Blood 4938 (2012).

[61] Laura J. Sauvé et al., Postvaccination Thrombocytopenia in Canada, 29 Pediatric Infectious Disease J. 559 (2010).

The second study was from Rajantie et al.[62] and reviewed data of children diagnosed with ITP in Nordic countries during a three-year period. Resp. Ex. G at 1. Of 506 pediatric ITP patients, the authors identified 35 patients that developed ITP within one month after vaccination. Id. Regarding this study, Dr. Baumann Kreuziger said "35 had an immunization within one month of the onset of ITP, but none of the cases were associated with the [flu] vaccine." Resp. Ex. A at 5. However, the flu vaccine was not identified as being administered to the study population. Resp. Ex. G at 2.

ii. Althen Prongs Two and Three

Dr. Baumann Kreuziger agreed with Petitioner's diagnosis of chronic ITP. Resp. Ex. A at 3. However, she disagreed that Petitioner's flu vaccine was the cause of her ITP. Id. Instead, Dr. Baumann Kreuziger offered two alternate causes for Petitioner's ITP: (1) an increased risk for development of ITP because of a history of thrombocytopenia and (2) a proceeding viral infection. Id. at 3-4.

The first alternate cause argument offered by Dr. Baumann Kreuziger is that "it is possible that [Petitioner] had an increased risk for development of ITP given her history of thrombocytopenia." Resp. Ex. A at 3. She referenced Petitioner's medical records from 2013 that showed Petitioner had a platelet count of 137,000. Id. (citing Pet. Ex. 12 at 8). Dr. Baumann Kreuziger agreed that "[c]urrent consensus guidelines recommend a platelet count <100,000 to diagnose ITP." Id. (citing Resp. Ex. H at 2 ("A platelet count less than 100 x 10^9/L was established as a threshold for diagnosis.")).

Although she appeared to agree that Petitioner did not meet the criteria for ITP based on her platelet count in 2013, Dr. Baumann Kreuziger explained that "having a platelet count <150,000 has been shown to be associated with the development of ITP." Resp. Ex. A at 3. She cited a cohort study from Stasi et al.,[63] in which 191 healthy individuals with platelet counts between 100 x 10^9/ L and 150 x 10^9/L were monitored for six months. Resp. Ex. J at 1. During the study, 12 of these individuals developed ITP, and the probability of developing ITP after 10 years was 6.9%. Id. at 4. Dr. Baumann Kreuziger asserted "[t]his is significantly higher than the incidence of ITP in the general population." Resp. Ex. A at 3 (citing Resp. Ex. K at 2).

Regarding an alternative cause, Dr. Baumann Kreuziger noted that Petitioner was treated with azithromycin (Z-pak) for an infection when she was diagnosed with ITP. Resp. Ex. A at 4-5. She observed that Petitioner's treating physician, Dr. Kale, suggested an association between Petitioner's viral infection and ITP. Id. However, Dr. Baumann Kreuziger did not opine that, more likely than not, Petitioner had an infection which triggered her ITP.

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[62] J. Rajantie et al., Vaccination Associated Thrombocytopenic Purpura in Children, 25 Vaccine 1838 (2007).

[63] Roberto Stasi et al., Long-Term Outcome of Otherwise Healthy Individuals with Incidentally Discovered Borderline Thrombocytopenia, 3 PLoS Med. e24 (2006).

Dr. Baumann Kreuziger also stated that none of Petitioner's treating physicians documented that there was an association between her flu vaccine and ITP. Resp. Ex. A at 5.

Lastly, Dr. Baumann Kreuziger did not refute the opinions by Petitioner's experts that there was a temporal association between Petitioner's vaccination and the onset of her ITP. However, she opined that "to a reasonable degree of probability, the occurrence of ITP in [Petitioner] was an incidental event and not caused by the [flu] vaccine that she received on [October 9, 2016]." Resp. Ex. at A at 5.

4. Respondent's Expert, Dr. Neil Romberg[64]

a. Background and Qualifications

Dr. Romberg currently works as an Assistant Professor of Pediatrics at the University of Pennsylvania School of Medicine and as an attending physician at the Children's Hospital of Philadelphia. Resp. Ex. M at 1; Resp. Ex. N at 1. Dr. Romberg attended Pennsylvania State University, College of Medicine and received his M.D. in 2004. Resp. Ex. N at 1. He then completed his pediatric residency at New York University, School of Medicine and a fellowship in allergy and clinical immunology at Yale University, School of Medicine. Id. He is board certified in pediatrics and allergy and immunology. Id. at 2. "The focus of [his] career has been the care for patients with inherited immunological disorders and to investigate the molecular mechanisms that underlie their diseases." Resp. Ex. M at 1-2. "Over the last 5 years [he] ha[s] cared for approximately 75 patients with an autoimmune cytopenia, either ITP or autoimmune hemolytic anemia (AIHA) or the overlap condition, Evans Syndrome." Id. at 2. Dr. Romberg has authored or co-authored over 30 publications. Resp. Ex. N at 7-12.

b. Opinion

Consistent with the other experts, Dr. Romberg agreed with Petitioner's diagnosis. Resp. Ex. M at 3-5. He explained that "ITP-associated platelet destruction is mediated by autoantibodies which 'flag' cells for splenic destruction." Id. at 5. Dr. Romberg opined that ITP has genetic predispositions and external triggers, including several infectious diseases such as HIV, hepatitis B virus, and hepatitis C virus. Id. at 6 (citing Pet. Ex. 20(a) at 4). ITP cases can be described as acute or chronic. Id. Acute episodes resolve within 12 months and chronic cases last greater than 12 months. Id. Dr. Romberg classified Petitioner's ITP as chronic, primary ITP. Id.

i. Althen Prong One

Unlike Dr. Baumann Kreuziger, Dr. Romberg agreed with the theory of molecular mimicry. He agreed that it is "one popular theory" as to why some individuals develop certain autoimmune diseases and others do not. Resp. Ex. M at 7. Dr. Romberg cited a systematic

[64] Dr. Romberg provided one expert report. Resp. Ex. M.

review by Bhattacharjee and Banerjee,[65] which "analyze[d] the clinical profile and outcomes in a total of 45 cases of new-onset ITP in COVID-19 patients." Resp. Ex. O at 1. The study found that ITP could occur secondary to a Covid-19 infection. Id. at 9. One suggested pathogenesis was molecular mimicry. Id. at 6-7, 9.

In addition to Covid-19 infections, Dr. Romberg discussed the association between other infections and ITP. He cited a study by Zeller et al. that examined data from Nordic countries on over 500 children who were newly diagnosed with ITP from 1998 to 1999. Resp. Ex. Q at 2. More than half of the patients (292, 57.7%) had an infection within the four weeks preceding diagnosis. Id. at 3. These infections included viral upper respiratory infections, flu-like infections, unspecified fever, bacterial infections, and chickenpox. Id.

In addition to infections, Dr. Romberg agreed that there is evidence linking the MMR vaccine to ITP. Resp. Ex. M at 8. He cited a review by Di Pietrantonj et al.[66] that provided a thorough overview of both the MMR and varicella vaccines in children. Resp. Ex. T at 3. The review found "evidence supporting an association between MMR vaccine and [ITP]." Id. at 4. Dr. Romberg agreed that the "MMR vaccine likely conveys an increased ITP risk." Resp. Ex. M at 8. He cited a study from France et al.,[67] in which the authors used data from 1991-2000 from the Vaccine Safety Datalink ("VSD") to examine the association between MMR and ITP. Resp. Ex. R at 1-2. Data were reported on children under 18 with a platelet count of less than or equal to 50,000/μL, clinical symptoms of spontaneous bleeding, and no fever. Id. at 2. The results of the study confirmed an association between ITP and the MMR vaccine. Id. at 6.

While Dr. Romberg acknowledged the association between the MMR vaccine and ITP, he opined that association does not extend to any other vaccine, including the seasonal flu vaccine. Resp. Ex. M at 8-9. He cited several studies supporting his opinion.[68] Id. at 8-11. One was from O'Leary et al.,[69] a retrospective cohort study of 1.8 million children who were vaccinated at one of five health care Kaiser Permanente Health Care Systems from 2000 to 2009. Resp. Ex. S at 2. They identified 197 cases of ITP, mostly attributable to the MMR vaccine. Id. at 3-5. For hepatitis A vaccine, there was a significantly increased risk of ITP in children seven

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[65] Sukrita Bhattacharjee & Mainak Banerjee, Immune Thrombocytopenia Secondary to COVID-19: A Systemic Review, 2 SN Comprehensive Clinical Med. 2048 (2020).

[66] C. Di Pietrantonj et al., Vaccines for Measles, Mumps, Rubella, and Varicella in Children (Review), Cochrane Database Systemic Revs. (2020).

[67] Eric K. France et al., Risk of Immune Thrombocytopenic Purpura After Measles-Mumps-Rubella Immunization in Children, 121 Pediatrics e687 (2008).

[68] Some of the studies cited by Dr. Romberg were also referenced by Dr. Baumann Kreuziger, and discussed above, and thus, will not be repeated here.

[69] Sean T. O'Leary et al., The Risk of Immune Thrombocytopenic Purpura After Vaccination in Children and Adolescents, 129 Pediatrics 248 (2012).

to 17 years of age, and for Tdap and varicella vaccines, there was a significantly increased risk of ITP in children 11 to 17 years of age. Id. at 1, 5, 5 tbl.2. O'Leary et al. noted that the study was limited by methodologies used to study rare adverse events. Id. at 6. Of note, the authors "found several elevated [incident rate ratios] that approached statistical significance in older children," including for the flu vaccine, but they concluded that "estimates in older children are less stable because there are fewer cases of ITP on which to perform analyses." Id. at 4. Additionally, of the children with ITP, it appears that many were not exposed to the flu vaccine. See id. at 5 tbl.2.

In addition to citing studies, Dr. Romberg also referenced the vaccine package insert for the Fluarix Quadrivalent Vaccine, 2019-2020 formula.[70] Resp. Ex. V. Clinical trial data from randomized, controlled studies establishing the safety of the Fluarix vaccine were provided. Id. at 5-14. Dr. Romberg noted that the studies did not report ITP. Resp. Ex. M at 8-9.

Dr. Romberg also dismissed the case reports and case series cited by Petitioner's experts. Resp. Ex. M at 9. Regarding Petitioner's reliance on this type of evidence, Dr. Romberg cited an article by Murad et al.,[71] where the authors proposed a tool "to evaluate the methodological quality" of this type of evidence. Resp. Ex. W at 1, 3. They did not reject the use of case reports, but instead "suggest[ed] using evidence derived from case reports and case series to inform decision-making when no other higher level of evidence is available." Id. at 1. Further, they provided examples of how case reports provide a valuable role by describing new diseases, unknown side effects of medication, novel treatments, providing education, and by the role they play in quality improvement. Id. at 3 tbl.2.

Regarding the causal mechanism of molecular mimicry, Dr. Romberg rejected the specific suggestion that flu vaccine proteins or platelet glycoproteins could act as molecular mimics and cause ITP. Resp. Ex. M at 10-11. He cited an article by Ang et al.[72] that used GBS as an "paradigm for how post-infectious immune-mediated disease in humans can be triggered by molecular mimicry." Resp. Ex. P at 1. The authors also suggested criteria for determining when molecular mimicry has triggered an immune-mediated disease: (1) "establishment of an epidemiological association between an infectious agent and the immune-mediated disease;" (2) "identification of T cells or antibodies directed against host target antigens in patients;" (3) "identification of microbial mimic of target antigen;" and (4) "reproduction of the disease in an animal model." Id. at 2-5.

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[70] This is not the formula that Petitioner received. Petitioner received her Fluarix vaccine in 2016. The package insert filed states that the "safety experience with FLUARIX (trivalent [flu] vaccine) is relevant to FLUARIX QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions." Resp. Ex. V at 5.

[71] Mohammad Hassan Murad et al., Methodological Quality and Synthesis of Case Series and Case Reports, 23 BMJ Evidence-Based Med. 60 (2018).

[72] C. Wim Ang et al., The Guillain-Barré Syndrome: A True Case of Molecular Mimicry, 25 Trends in Immunology 61 (2004).

Dr. Romberg opined "GBS and ITP are completely distinct autoimmune processes; the former is driven by T-cell responses to peripheral nerve gangliosides while the latter is mediated by autoantibodies to platelet glycoproteins." Resp. Ex. M at 10. Dr. Romberg dismissed Petitioner's experts' reliance on the article by Isai et al., which found molecular mimicry to be a mechanistic theory for the development of ITP. Id. (citing Pet. Ex. 20(n)). Dr. Romberg rejected this because the article "did not find ITP cases . . . to be more than expected." Id. Therefore, he concluded that the article failed to find an epidemiological association between the vaccine and ITP. Id.

Dr. Romberg also dismissed the theory that HA was the molecular mimic that leads to ITP. He explained that the theory assumes that ITP occurs when "HA protein entered the blood stream, bound platelets without harming them but instead marked them for destruction by HA-specific antibodies." Resp. Ex. M at 10. He criticized Petitioner's expert's reliance on the article written by Dr. Shoenfeld and dismissed this theory because (1) "this is not an example of molecular mimicry, as the antibody is not to a self-antigen but to a microbial one," and (2) this theory "cannot explain the chronic nature of [Petitioner's] ITP."[73] Id. (citing Pet. Ex. 20(o)) (emphasis omitted). Dr. Romberg cited an article by Sahler et al.[74] to explain that the lifespan of platelets is about 8-10 days, and therefore, they are continuously regenerated to maintain levels of at least 150,000 per microliter of blood. Resp. Ex. Z at 1. Therefore, Dr. Romberg claimed, "even if the small amount of HA protein administered by the intramuscular route did enter her blood stream and bind to all of her platelets on October 9, 2016, these HA-bound cells would have been destroyed and replaced several times over by December 7, 2016." Resp. Ex. M at 10-11.

Finally, Dr. Romberg opined that the vaccination lowered Petitioner's risk of developing ITP. He cited a literature review that recommended patients with ITP get vaccinated because the therapies used to treat ITP are immunosuppressive. Resp. Ex. BB at 3.[75] In addition, Dr. Romberg cited a review by Elalfy and Nugent[76] that provided a broad overview of the association between viral infections, anti-viral therapy, and viral vaccines with ITP. Resp. Ex. AA at 1. Elalfy and Nugent noted that "the incidence of post-immunization ITP is significantly lower than that observed during the natural disease that" vaccines prevent. Id. at 2.

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[73] Respondent also criticized Petitioner's reliance on articles written by Dr. Yehuda Shoenfeld because some of Dr. Shoenfeld's articles have been withdrawn from publication. Resp. Ex. M at 9. However, none of the withdrawn articles were relied on by Petitioner's experts.

[74] Julie Sahler et al., Platelet Storage and Transfusions: New Concerns Associated with an Old Therapy, 8 Drug Discovery Today Disease Mechanisms e9 (2011).

[75] Donald M. Arnold et al., Immune Thrombocytopenia (ITP) in Adults: Initial Treatment and Prognosis, UpToDate, https://www.uptodate.com/contents/initial-treatment-of-immune-thrombocytopenia-itp-in-adults (last updated Sept. 20, 2019).

[76] Mohsen S. Elalfy & Diane Nugent, Viruses, Anti-Viral Therapy, and Viral Vaccines in Children with Immune Thrombocytopenia, 53 Seminars Hematology S70 (2016).

In conclusion, Dr. Romberg agreed that molecular mimicry is a causal theory. Resp. Ex. M at 7. He agreed that ITP has been associated with viral infections and some vaccines, including the MMR vaccine. Id. at 7-8. However, Dr. Romberg did not agree that there is evidence the flu vaccine can cause ITP. Id. at 8. Specifically, Dr. Romberg dismissed the theory that flu vaccine proteins and/or platelet glycoproteins could act as molecular mimics to cause ITP. Id. at 10.

ii. Althen Prongs Two and Three

Dr. Romberg did not agree that Petitioner's flu vaccine was the cause of her ITP. Resp. Ex. M at 8-11. Dr. Romberg suggested Petitioner's history of throat infections, upper respiratory infections, or other viral infections she was "predisposed to" by working in day care was an alternative cause of Petitioner's ITP. Id. at 11. He reiterated evidence showing that viral infections can cause ITP. Id.

He noted that Petitioner reported sinus symptoms on December 7, 2016, and she was prescribed a Z-pak. Resp. Ex. M at 11. Petitioner's hematologist, Dr. Kale, also reported she had an upper respiratory infection on December 12, 2016. Id. Dr. Romberg opined that "a proceeding viral infection [is], by far, the most likely trigger of [Petitioner's] ITP." Id.

Dr. Romberg did not offer an opinion about the temporal relationship between the vaccine and onset of Petitioner's ITP. He did not refute Petitioner's expert opinions stating that there was an appropriate time frame between vaccination and the onset of Petitioner's ITP given the mechanism of molecular mimicry.

IV. DISCUSSION

A. Standards for Adjudication

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Hum. Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioner's burden of proof is by a preponderance of the evidence. § 13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, Petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

Petitioner must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Hum. Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); see also Pafford v. Sec'y of Health & Hum. Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). The received vaccine, however, need not be the predominant cause of the injury. Shyface, 165 F.3d at 1351. A petitioner who satisfies this burden is entitled to compensation unless Respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B). However, if a petitioner fails to establish a prima facie case, the burden does not shift. Bradley v. Sec'y of Health & Hum. Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

"Regardless of whether the burden ever shifts to the [R]espondent, the special master may consider the evidence presented by the [R]espondent in determining whether the [P]etitioner has established a prima facie case." Flores v. Sec'y of Health & Hum. Servs., 115 Fed. Cl. 157, 162-63 (2014); see also Stone v. Sec'y of Health & Hum. Servs., 676 F.3d 1373, 1379 (Fed. Cir. 2012) ("[E]vidence of other possible sources of injury can be relevant not only to the 'factors unrelated' defense, but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question."); de Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008) ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the [P]etitioner's evidence on a requisite element of the [P]etitioner's case-in-chief."); Pafford, 451 F.3d at 1358-59 ("[T]he presence of multiple potential causative agents makes it difficult to attribute 'but for' causation to the vaccination. . . . [T]he Special Master properly introduced the presence of the other unrelated contemporaneous events as just as likely to have been the triggering event as the vaccinations.").

B. Factual Issues

A petitioner must prove, by a preponderance of the evidence, the factual circumstances surrounding her claim. § 13(a)(1)(A). To resolve factual issues, the special master must weigh the evidence presented, which may include contemporaneous medical records and testimony. See Burns v. Sec'y of Health & Hum. Servs., 3 F.3d 415, 417 (Fed. Cir. 1993) (explaining that a special master must decide what weight to give evidence including oral testimony and contemporaneous medical records). Contemporaneous medical records, "in general, warrant consideration as trustworthy evidence." Cucuras v. Sec'y of Health & Hum. Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993). But see Kirby v. Sec'y of Health & Hum. Servs., 997 F.3d 1378, 1382 (Fed. Cir. 2021) (rejecting the presumption that "medical records are accurate and complete as to all the patient's physical conditions"); Shapiro v. Sec'y of Health & Hum. Servs., 101 Fed. Cl. 532, 538 (2011) ("[T]he absence of a reference to a condition or circumstance is much less significant than a reference which negates the existence of the condition or circumstance." (quoting Murphy v. Sec'y of Health & Hum. Servs., 23 Cl. Ct. 726, 733 (1991), aff'd per curiam, 968 F.2d 1226 (Fed. Cir. 1992))), recons. den'd after remand, 105 Fed. Cl. 353 (2012), aff'd mem., 503 F. App'x 952 (Fed. Cir. 2013).

There are situations in which compelling testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. Campbell v. Sec'y of

Health & Hum. Servs., 69 Fed. Cl. 775, 779 (2006) ("[L]ike any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking."); Lowrie v. Sec'y of Health & Hum. Servs., No. 03-1585V, 2005 WL 6117475, at *19 (Fed. Cl. Spec. Mstr. Dec. 12, 2005) ("[W]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent." (quoting Murphy v. Sec'y of Health & Hum. Servs., 23 Cl. Ct. 726, 733 (1991), aff'd per curiam, 968 F.2d 1226 (Fed. Cir. 1992))). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. Andreu v. Sec'y of Health & Hum. Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009); Bradley, 991 F.2d at 1575.

Despite the weight afforded medical records, special masters are not bound rigidly by those records in determining onset of a petitioner's symptoms. Valenzuela v. Sec'y of Health & Hum. Servs., No. 90-1002V, 1991 WL 182241, at *3 (Fed. Cl. Spec. Mstr. Aug. 30, 1991); see also Eng v. Sec'y of Health & Hum. Servs., No. 90-1754V, 1994 WL 67704, at *3 (Fed. Cl. Spec. Mstr. Feb. 18, 1994) (Section 13(b)(2) "must be construed so as to give effect also to § 13(b)(1) which directs the special master or court to consider the medical records (reports, diagnosis, conclusions, medical judgment, test reports, etc.), but does not require the special master or court to be bound by them").

C. Causation

To receive compensation through the Program, Petitioner must prove either (1) that she suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that she received, or (2) that she suffered an injury that was caused by a vaccination. See §§ 11(c)(1), 13(a)(1)(A); Capizzano, 440 F.3d at 1319-20. Petitioner must show that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface, 165 F.3d at 1352-53).

Because Petitioner does not allege she suffered a Table Injury, she must prove a vaccine she received caused her injury. To do so, Petitioner must establish, by preponderant evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278.

The causation theory must relate to the injury alleged. Petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d. 543, 548-49 (Fed. Cir. 1994). Petitioner cannot establish entitlement to compensation based solely on her assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether Petitioner is entitled to compensation, the special master shall consider all material in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in Petitioner's favor when the evidence weighs in her favor. See Moberly, 592 F.3d at 1325-26 ("Finders of

fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); Althen, 418 F.3d at 1280 (noting that "close calls" are resolved in Petitioner's favor).

Testimony that merely expresses the possibility—not the probability—is insufficient, by itself, to substantiate a claim that such an injury occurred. See Waterman v. Sec'y of Health & Hum. Servs., 123 Fed. Cl. 564, 573-74 (2015) (denying Petitioner's motion for review and noting that a possible causal link was not sufficient to meet the preponderance standard). The Federal Circuit has made clear that the mere possibility of a link between a vaccination and a petitioner's injury is not sufficient to satisfy the preponderance standard. Moberly, 592 F.3d at 1322 (emphasizing that "proof of a 'plausible' or 'possible' causal link between the vaccine and the injury" does not equate to proof of causation by a preponderance of the evidence); Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359-60 (Fed. Cir. 2019); . While certainty is by no means required, a possible mechanism does not rise to the level of preponderance. Moberly, 592 F.3d at 1322; see also de Bazan, 539 F.3d at 1351.

V. CAUSATION ANALYSIS

A. Althen Prong One

Under Althen Prong One, Petitioner must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreu, 569 F.3d at 1375; Pafford, 451 F.3d at 1355-56. Petitioner's theory of causation need not be medically or scientifically certain, but it must be informed by a "sound and reliable" medical or scientific explanation. Boatmon, 941 F.3d at 1359; see also Knudsen, 35 F.3d at 548; Veryzer v. Sec'y of Health & Hum. Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If Petitioner relies upon a medical opinion to support her theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec'y of Health & Hum. Servs., 618 F.3d 1339, 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Hum. Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it" (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980))).

For the following reasons, the undersigned finds Petitioner provided preponderant evidence that the flu vaccination she received caused her ITP, and therefore, Petitioner satisfied the first Althen prong.

All the experts agree, and many of the medical articles filed, establish that ITP is known to be an autoimmune condition, and that at least as it relates to infectious triggers, molecular mimicry is a likely causal mechanism. See, e.g., Pet. Ex. 15 at 9; Pet. Ex. 18 at 3; Resp. Ex. A at 4; Resp. M at 7. For example, Perera and Garrido found the trigger of ITP to be "loss of tolerance due to molecular mimicry with cross-reaction of antibodies arising from infectious

agents or drugs, genetic factors, and/or platelet Toll receptors." Pet. Ex. 20(m) at 2. Swinkels et al. noted that "[o]ne of the suggested mechanisms by which infections lead to autoimmunity is the occurrence of molecular mimicry." Resp. Ex. K at 3. Cooper and Bussel reported that "[c]hildhood ITP often occurs following a viral illness," with the infection initiating ITP "probably" through molecular mimicry. Pet. Ex. 33 at 6. In Zeller et al., more than half the patients had an infection four weeks before they were diagnosed with ITP. Resp. Ex. Q at 3. The most common infections included viral upper respiratory infections, flu-like diseases, or unspecified fever. Id. Finally, Bhattacharjee and Banerjee suggested "SARS-CoV-2-mediated immune thrombocytopenia can be attributed to . . . mechanisms, including molecular mimicry." Resp. Ex. O at 1.

More specifically, flu infections have been associated with ITP via molecular mimicry. Rinaldi et al. reported a case of ITP following "[a] case of 2009 H1N1 symptomatic [flu] A virus infection." Pet. Ex. 17(d) at 5. Kazatchkine et al. found platelets treated with flu A displayed viral HA and were destroyed by immune cells. Resp. Ex. E at 1. Lee et al. reported the case of a patient who developed "extensive cutaneous petechiae, ecchymosis[,] and painful bleeding of the mouth" three days into an "[flu]-like illness." Pet. Ex. 20(i) at 2. The patient's infection was confirmed to be the 2009 H1N1 flu A virus. Id. at 3. Kosugi et al.[77] reported a patient who was diagnosed with thrombotic thrombocytopenic purpura ("TTP")[78] two days after she was diagnosed with flu A. Pet. Ex. 20(j) at 1. Finally, Ning et al.[79] also reported a patient who developed TTP following a flu A (H1N1) infection. Pet. Ex. 20(k) at 1-2.

Petitioner's experts provided sound and reliable reasons for extending the application of molecular mimicry from infections to vaccinations, and again cited supportive medical literature. Perricone et al. described the "most likely" mechanism whereby vaccines cause ITP is "molecular mimicry." Pet. Ex. 17(e) at 1. Cecinati et al. stated that ITP after vaccination is caused by the "development of autoantibodies that cross-react with the naturally present antigenic targets on platelets." Pet. Ex. 17(p) at 1.

Moreover, as compared with the paucity of medical literature regarding many alleged post-vaccination adverse conditions, there is a wealth of medical literature that supports an association between vaccinations and ITP. Further, there is a known causal association between

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[77] Nobuharu Kosugi et al., Influenza A Infection Triggers Thrombotic Thrombocytopenic Purpura by Producing the Anti-ADAMTS13 IgG Inhibitor, 49 Internal Med. 689 (2010).

[78] Thrombotic thrombocytopenic purpura is "a form of thrombotic microangiopathy usually seen in adults, characterized by thrombocytopenia with thromboses in terminal arterioles and capillaries; other symptoms include hemolytic anemia, azotemia, fever, and bizarre neurologic manifestations." Thrombotic Thrombocytopenic Purpura, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=101175 (last visited Dec. 27, 2022).

[79] Junjie Ning et al., Case of Acquired Thrombotic Thrombocytopenic Purpura Associated with Influenza A (H1N1) Virus and Literature Review, 57 J. Paediatrics & Child Health 282 (2020). Only the first page of this article was filed.

the MMR vaccine and ITP, and that association is reflected in the Vaccine Injury Table.[80] While the presumption of causation for ITP following the MMR vaccine has not been extended to other vaccines, the evidence filed here supports vaccine causation as to the flu vaccine.

And more narrowly, and specific to the facts of this case, Petitioner provided preponderant evidence, by expert opinion and medical literature, of an association between the flu vaccine and ITP. Garbe et al. reported that "[flu] vaccination was associated with a statistically significant [four]-fold risk" of developing ITP. Pet. Ex. 17(f) at 9. The study by Jadavji et al. reported 61 admissions of ITP following vaccination; two of which occurred after the flu vaccine. Pet. Ex. 17(l) at 2. Perricone et al. summarized the available studies and case reports and concluded there was a link between ITP and the flu vaccine. Pet. Ex. 17(e) at 4.

Further, there is evidence that molecular mimicry is a sound and reliable mechanism by which the flu vaccine can cause ITP. Perricone et al. stated that molecular mimicry is the likely mechanism by which the flu vaccine triggers ITP. Pet. Ex. 17(e) at 4. Petitioner's experts also cited case studies in which patients developed ITP following flu vaccination and the authors postulated the mechanistic cause was molecular mimicry. See, e.g., Pet. Ex. 17(g) at 2; Pet. Ex. 17(h) at 1; Pet. Ex. 17(k) at 2; Pet. Ex. 17(m) at 1-2; Pet. Ex. 17(n) at 2; Pet. Ex. 17(o) at 2; Pet. Ex. 20(r) at 3; Pet. Ex. 20(t) at 2.

Petitioner's experts also provided evidence as to the target of molecular mimicry. Perricone et al. explained that "[i]n [flu], the target of molecular mimicry probably involves [HA]." Pet. Ex. 17(e) at 4. David and Shoenfeld stated that "[t]he main antigen in the [flu] vaccine, [HA], is believed to be one of the possible molecules involved" in "immunization causing ITP by molecular mimicry." Pet. Ex. 20(o) at 1. In addition, Wan Jamaludi et al.[81] concluded relative to the flu vaccine and ITP, that "the target of molecular mimicry probably involves [HA]." Id. at 2.

In addition, Petitioner's experts cite numerous case studies reporting the development of ITP following the flu vaccine.[82] Respondent's experts argued case reports should not be relied on as evidence of an association between ITP and the flu vaccine and cited literature that discusses the reliability of case reports and case series. See Resp. Ex. C at 1. Resp. Ex. W at 1. While case reports alone do not establish causation, here there are studies by Garbe et al. and Perricone et al. and numerous case reports.

Moreover, the undersigned finds the Hamiel et al. and Almohammadi et al. case reports to be very persuasive evidence of causation. Hamiel et al. described the case of a child who developed ITP three times, each time after a flu vaccination. The authors concluded that they were "the first to show with a high degree of confidence an association between the trivalent

[80] See 42 C.F.R. §§ 100.3(a)(V)(A), (c)(7).

[81] WF Wan Jamaludin et al., Vaccine-Induced Immune Thrombocytopaenia Purpura in Autologous Haematopoietic Stem Cell Transplantation, 73 Med. J. Malay. 430 (2018).

[82] See Pet. Exs. 17(g)-17(k), 17(m)-17(o); Pet. Exs. 20(r), 20(v).

[flu] vaccine and the development of ITP. The response to IVIG therapy strongly suggests an immunologic mechanism . . . ." Pet. Ex. 20(r) at 3. Almohammadi et al. also described an adult who had episodes of epistaxis after receipt of the flu vaccines on three consecutive occasions. Pet. Ex. 20(t) at 1. These facts of these two case reports were interpreted by the authors as very compelling evidence that the flu vaccine can cause ITP.

Additionally, the above case reports may represent evidence of rechallenge. "A 'challenge/rechallenge' circumstance exists when a person has a reaction to one administration of a vaccine or drug and then suffers worsening symptoms after an additional administration of the same vaccine or drug."[83] Hirmiz v. Sec'y of Health & Hum. Servs., 119 Fed. Cl. 209, 219 n.11 (2015); see also DePena v. Sec'y of Health & Hum. Servs., 133 Fed. Cl. 535, (2017) (describing challenge/rechallenge as "when an individual . . . exhibits a more severe reaction to a second administration of that vaccine"). Additionally, Congress stated that "[a]n adverse event can be causally linked to a vaccine more readily if: . . . the event recurs on re-administration of the vaccine (positive rechallenge)." H.R. Rep. No. 106-977, at 5 (2000).

In summary, Petitioner has offered a sound and reliable medical theory in support of her claim. Thus, the undersigned finds Petitioner has provided preponderant evidence with respect to the first Althen prong.

B. Althen Prong Three

A discussion of Althen Prong Two turns to some extent on the question of onset of Petitioner's ITP as well as the onset of her upper respiratory infection. Therefore, the undersigned addresses Althen Prong Three before moving to Althen Prong Two.

Althen Prong Three requires Petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281. That term has been defined as a "medically acceptable temporal relationship." Id. Petitioner must offer "preponderant proof that the onset of symptoms occurred within a time frame for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under Althen Prong One). Id.; Koehn v. Sec'y of Health & Hum. Servs., 773 F.3d 1239, 1243 (Fed. Cir. 2014); Shapiro, 101 Fed. Cl. at 542; see Pafford, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. See, e.g., Veryzer, 100 Fed. Cl. at 356 (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that

[83] "An important attribute in the evaluation of the clinical evidence from case reports is *rechallenge*, an adverse event that occurred after more than one administration of a particular vaccine in the same individual. Each challenge in a patient, however, must meet the same attributes of reasonable latency, documentation of vaccination receipt, and clinician diagnosis of the health outcome." Inst. of Med., Summary, in Adverse Effects of Vaccines: Evidence and Causality 1, 13 (Kathleen Stratton et al. eds., 2012).

[P]etitioner must posit a medical theory causally connecting the vaccine and injury"), aff'd, 475 F. App'x 765 (Fed. Cir. 2012).

The events leading up to Petitioner's diagnosis of ITP are described in Petitioner's affidavits. She received the flu vaccination at issue on October 9, 2016, and observed bruising on the front and back of her thighs in mid-November, two weeks before her birthday on November 27, 2016. Dr. Serota opined, based on Petitioner's affidavit and a review of her medical records, that Petitioner began to experience symptoms of her ITP around November 13, 2016, approximately 35 days after she received her flu vaccine.

Dr. Ghose opined that onset of ITP occurs within four to 35 days following flu vaccination. Cecinati et al. reported that "vaccine-related ITP usually occurs within six weeks of vaccination." Pet. Ex. 17(p) at 2. Dr. Ghose also cited seven case reports of nine patients who developed ITP between 4 and 35 days after receiving a flu vaccination. See Pet. Ex. 17(g) at 1-2; Pet. Ex. 17(h) at 1; Pet. Ex. 17(i) at 1; Pet. Ex. 17(j) at 1; Pet. Ex. 17(m) at 1-2; Pet. Ex. 17(n) at 1-2; Pet. Ex. 17(o) at 1. One of these, authored by Nagasaki et al., contained three case reports of patients whose onset of ITP occurred at two, four, and five weeks after flu vaccination. Pet. Ex. 20(g) at 1-2. Neither Dr. Baumann Kreuziger nor Dr. Romberg provided evidence to contradict Dr. Ghose and Dr. Serota's timeline of onset or that onset was appropriate given the theory of molecular mimicry.

Therefore, undersigned finds that onset occurred approximately 35 days after vaccination, around November 13, 2016, and that this time frame is appropriate given the mechanism of molecular mimicry. Therefore, Petitioner has met her burden of proof as to Althen Prong Three.

C. Althen Prong Two

Under Althen Prong Two, Petitioner must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (internal citations omitted).

In evaluating whether this prong is satisfied, the opinions and views of the vaccinee's treating physicians are entitled to some weight. Andreu, 569 F.3d at 1367; Capizzano, 440 F.3d at 1326 ("[M]edical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause-and-effect show[s] that the vaccination was the reason for the injury.'" (quoting Althen, 418 F.3d at 1280)). Medical records are generally viewed as trustworthy evidence, since they are created contemporaneously with the treatment of the vaccinee. Cucuras, 993 F.2d at 1528. Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano, 440 F.3d at 1325. Instead, Petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

The undersigned finds Petitioner has proved Althen Prong Two by preponderant evidence for the following reasons.

The evidence establishes that on December 5, 2016, Petitioner developed a stuffy nose and other cold-like symptoms. By that time, she was already experiencing bruising, dizziness, lightheadedness, fatigue, weakness, and heavy menstruation. On December 7, 2016, Petitioner visited her OB/GYN where she underwent a full panel of blood work. Her physician prescribed a Z-pak on that date for her cold symptoms. The next day, on December 8, Petitioner's physician notified her that her platelets were critically low at 12,000.

Dr. Serota opined that Petitioner developed ITP as a result of the antigenic exposure to the flu vaccine she received. As described above, based on Petitioner's affidavit and medical records, Dr. Serota found the onset of Petitioner's ITP was approximately November 13, 2016. He also determined that Petitioner's upper respiratory infection began on December 5, 2016, when she began experiencing cold symptoms that required her doctor to prescribe the Z-pak. Since Petitioner's bleeding symptoms began several weeks before her viral infection, Dr. Serota opined that her viral infection could not have caused her ITP. While both Dr. Baumann Kreuziger and Dr. Romberg opine that Petitioner's viral infection was the most likely trigger of her ITP, neither offered evidence to refute the timeline described in Petitioner's affidavit or medical records, or the timeline described by Dr. Serota.

Thus, based on the chronology of events set forth in the Petitioner's affidavit and medical records, as well as the opinion of Dr. Serota consistent with the evidence, the undersigned finds that the onset of Petitioner's ITP occurred before the onset of her viral illness. Further, the undersigned finds that there is no evidence that Petitioner had a viral infection before the onset of her bleeding symptoms in mid-November.

This finding is not necessarily inconsistent with the opinions of Petitioner's hematologist, Dr. Kale. Dr. Kale initially diagnosed Petitioner with a differential diagnosis of "[s]evere thrombocytopenia likely immune thrombocytopenia versus thrombocytopenia due to recent viral upper respiratory tract infection." Pet. Ex. 4 at 12. Dr. Kale suggested that Petitioner's ITP "[c]ould be from an acute viral upper respiratory infection which hopefully will improve over time and not cause chronic ITP." Id. By March 2017, however, Dr. Kale dropped the reference to "thrombocytopenia due to viral illness." Instead, the sole diagnosis was "severe labile immune thrombocytopenia (ITP)." Id. at 77. Dr. Kale no longer documented that a viral infection could have been the cause of her illness.

Further, while Dr. Kale did not note an association between her vaccination and ITP, it does not appear that he was aware that Petitioner's bruising began in November 2016, or that she had received a vaccination prior to the onset of her ITP. Dr. Kale's history does not include the date that Petitioner's bleeding symptoms began or the date on which Petitioner began having cold symptoms. Dr. Kale's history also does not include the fact that Petitioner had previously received a flu vaccine. After considering all the evidence, the opinion made by Dr. Kale that Petitioner may have had ITP due to a viral illness appears to be based on an incomplete knowledge of the facts, and therefore, the undersigned gives it less weight.

Given the undersigned's findings on onset, the undersigned also finds that Petitioner's clinical course is consistent with post-vaccination ITP. She received her flu vaccine on October 9, 2016, and developed bruising approximately November 13, 2016. When she saw her gynecologist on December 7, she described a heavy menstrual period that had lasted eight days. Blood work showed very low platelet levels. This clinical course is consistent with ITP following vaccination as described in the medical literature and case reports. See, e.g., Pet. Ex. 17(g) at 1-2 (describing a case of a woman who reported genital bleeding and purpura two weeks after a flu vaccination and was diagnosed with ITP, and another case of a woman who "experienced massive bleeding" that was diagnosed as ITP and began five weeks following a flu vaccination); Pet. Ex. 17(h) (describing a man who developed severe thrombocytopenia with gastrointestinal bleeding two weeks after administration of a flu vaccine).

Regarding Dr. Baumann Kreuziger's opinion that Petitioner had a "possible" increased risk for development of ITP because of her history of thrombocytopenia,[84] the undersigned finds this opinion is only noted to be a possibility and thus, insufficient to establish an alternative cause for Petitioner's ITP. Moberly, 592 F.3d at 1322 (emphasizing that "proof of a 'plausible' or 'possible' causal link between the vaccine and the injury" does not equate to proof of causation by a preponderance of the evidence); Waterman, 123 Fed. Cl. at 573-74 (denying Petitioner's motion for review and noting that a possible causal link was not sufficient to meet the preponderance standard); Boatmon, 941 F.3d at 1359-60; Paterek v. Sec'y of Health & Hum. Servs., 527 F. App'x 875, 883 (Fed. Cir. 2013). While certainty is by no means required, a possible mechanism does not rise to the level of preponderance. Moberly, 592 F.3d at 1322; see also de Bazan, 539 F.3d at 1351.

Moreover, even if Dr. Baumann Kreuzier's opinion that Petitioner was at risk for ITP were true, this would simply make Petitioner more susceptible to developing ITP after vaccination. It would not defeat her claim for vaccine-related ITP.

Further, the medical literature does not support a finding that Petitioner's one time platelet count of 137,000 increased her risk of developing ITP. The Stasi et al. study cited by Dr. Baumann Kreuziger showed that the majority of those in the study did not develop ITP. "[A]t the end of the study, . . . the probability of developing ITP at 10 y[ears] was 6.9% . . . ."[85] Resp. Ex. J at 4. In addition, none of Petitioner's medical records support the conclusion she was diagnosed with thrombocytopenia in 2013. She was not informed about the platelet count or told that it was anything to be concerned about, and she was not referred to a hematologist for follow-up.

For all the reasons described above, the undersigned finds that Petitioner has provided preponderant evidence of a logical sequence of cause and effect required under Althen Prong Two.

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[84] Specifically, Dr. Baumann Kreuziger opined that "it is possible that [Petitioner] has an increased risk for development of ITP given her history of thrombocytopenia." Resp. Ex. A at 3.

[85] Stasi et al. also found "a 10 y[ear] probability of developing [an] autoimmune disorder[] [to be] 12%." Resp. Ex. J at 7.

D. Alternative Causation

Because the undersigned concludes that Petitioner has established a prima facie case, Petitioner is entitled to compensation unless Respondent can put forth preponderant evidence "that Petitioner's injury was in fact caused by factors unrelated to the vaccine." Whitecotton v. Sec'y of Health & Hum. Servs., 17 F.3d 374, 376 (Fed. Cir. 1994), rev'd on other grounds sub nom., Shalala v. Whitecotton, 514 U.S. 268 (1995); see also Walther v. Sec'y of Health & Hum. Servs., 485 F.3d 1146, 1151 (Fed. Cir. 2007). As discussed above in the analysis related to Althen Prong Two, the undersigned found Respondent failed to establish evidence to show that Petitioner's ITP was caused by a source other than vaccination. Thus, Respondent did not prove by a preponderance of evidence that Petitioner's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B).

VI. CONCLUSION

For the reasons discussed above, the undersigned finds that Petitioner has established by preponderant evidence that her flu vaccine caused her ITP. Therefore, Petitioner is entitled to compensation. A separate damages order will issue.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master